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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

Date: 04/30/2009

MEMORANDUM

SUBJECT: Pyraclostrobin: Human Health Risk Assessment for Proposed Uses on Grain Sorghum (PP#8F7385); Increase of Tolerance for the Stone Fruit Crop Group 12 to Satisfy European Union (EU) Import Requirement (PP#8F7390); and Establishment of a Permanent Import Tolerance for Coffee (PP#8E7394).

PC Code: 099100
Decision No.: 397102

Petition Nos.: 8F7385, 8F7390, and 8E7394
Risk Assessment Type: Single Chemical/Aggregate
TXR No.: NA
MRID Nos.: NA

DP Barcode: D356946
Registration No.: 7969-186, 7969-266, & 7969-199
Regulatory Action: Section 3 Registration Action
Case No.: NA

CAS No.: 175013-18-0
40 CFR: 180.582

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The Registration Division (RD) of the Office of Pesticide Programs (OPP) has requested that HED evaluate toxicology and residue chemistry data and conduct dietary, aggregate, and occupational exposure and risk assessments, as needed, to estimate the risk to human health that will result from existing and proposed uses of pyraclostrobin.

BASF Corporation submitted three separate petitions. In petition PP#8F7385, BASF requested the establishment of pyraclostrobin tolerances and the addition of new foliar and seed treatment uses on grain sorghum. In petition PP#8F7390, BASF requested an increase in the tolerance for the stone fruit crop group 12. In petition PP#8E7394, BASF requested the establishment of a tolerance for imported coffee.

The Health Effects Division (HED) has conducted a human health risk assessment for these proposed and changed uses. HED has high confidence in the quality of the toxicology, chemistry and exposure databases used to assess risk from pyraclostrobin.

A summary of the findings and an assessment of human risk resulting from the registered and proposed tolerances for pyraclostrobin are provided in this document. The risk assessment and the occupational/residential exposure assessment were provided by Barry O'Keefe. The residue chemistry data review and dietary risk assessment were provided by Meheret Negussie. The toxicology update was provided by Whang Phang.

Table of Contents

1.0 Executive Summary

Pyraclostrobin [carbamic acid, [2-[[[1-(4-chlorophenyl)-1*H*-pyrazol-3-yl]oxy]methyl] phenyl]methoxy-, methyl ester] (CAS nomenclature) belongs to the strobilurin class of fungicides (β-methoxyacrylate class of compounds). Strobilurins are synthetic analogs of a natural antifungal substance which inhibit spore germination, mycelial growth, and sporulation of the fungus on the leaf surface.

Pyraclostrobin is currently registered on barley, berries, *Brassica* vegetables, bulb vegetables, canola, citrus, corn (field, pop and sweet), cotton, cucurbit vegetables, flax, fruiting vegetables, grapes, grass grown for seed, hops, leafy vegetables, legumes (dried peas and beans, succulent shelled peas and beans), mint, oats, peanuts, pistachios, pome fruit, potatoes, root vegetables, rye, soybean, strawberries, stone fruits, sugar beets, sunflower, tropical fruits, tuberous and corm vegetables, tree nuts, and wheat, as well as ornamentals, and residential and golf course turf.

BASF Corporation submitted a petition (8F7385) requesting tolerances for residues of pyraclostrobin in/or on field grown sorghum; Headline® EC Fungicide (a liquid concentrate) EPA Reg. No. 7969-186. Only one application of Headline® EC Fungicide may be applied per season at 0.1 to 0.2 lb ai/A (6-12 fl oz/A) by aerial, chemigation, or groundboom equipment, with applications no later than the 25% flowering stage. In addition, the petitioner proposes to add a supplemental label to the seed treatment label, Stamina™ (a liquid concentrate) EPA Reg. No. 7969-266. Pyraclostrobin may be applied to sorghum seeds with commercial seed treatment equipment at 0.01 to 0.02 lb ai/100 lb of seed (0.8-0.15 fl oz/100 lb seed).

BASF Corporation submitted a petition (8F7390) requesting an increase in the tolerance for the stone fruit crop group 12 from 0.9 ppm to 2.5 ppm. Application of Pristine® Fungicide BAS 516 04F (EPA Reg. No. 7969-199) to stone fruits is proposed at 0.84 to 0.117 lb ai/A (10.5-14.5 fl oz/A) with up to five re-treatments at 7 to 14 day intervals up to a maximum seasonal application rate of 0.585 lb ai/a (72.5 fl oz/A) and with a 0-day PHI. Pristine® Fungicide is a WDG formulation containing the multiple active ingredients of pyraclostrobin (12.8%) and boscalid (25.2%).

BASF Corporation submitted a petition (8E7394) requesting the establishment of a tolerance for imported coffee. The supplemental COMET® 25% EC label is proposed (supplemental for the Headline® EC Fungicide (liquid concentrate) EPA Reg. No. 7969-186) at up to two applications at 0.1 to 0.2 lb ai/A (150-200 g/ha).

The Health Effects Division (HED) has conducted a human health risk assessment for these proposed and changed uses. HED has high confidence in the quality of the toxicology, chemistry and exposure databases used to assess risk from the use of pyraclostrobin.

Hazard Assessment Summary

The quality of the toxicology database for pyraclostrobin is good and the confidence in the hazard and dose-response assessments is high. The toxicity database for pyraclostrobin is considered adequate for endpoint selection for exposure risk assessment scenarios and for FQPA evaluation. Based on the hazard and exposure data, the RAB3 pyraclostrobin risk assessment team concluded that the FQPA safety factor can be reduced to 1X. Please refer to Appendix A for the toxicity profile tables. Please also refer to a previous pyraclostrobin risk assessment document for further extensive details (B. O'Keefe, DP Barcode 343700, 9/7/07). As there is no new toxicity data associated with these current actions, the hazard characterization and endpoint selection from the previous risk assessment are applied directly to this action. However, under the current 40 CFR §158.500 data requirement guidelines, the immunotoxicity data (OPPTS 780.7800) shall be required as a condition of registration.

Dietary (Food & Drinking Water) Exposure Assessment

Acute and chronic dietary exposure assessments were conducted for the proposed and existing food uses and drinking water inputs. These acute and chronic dietary risk assessments are considered only minimally refined.

The acute analysis was conducted using either tolerance level residues or highest residues derived from field trial data conducted at the maximum application rate and minimum PHI permitted on the proposed or existing labels. For all commodities 100% crop treated was assumed. A limited number of experimentally derived processing factors were used to refine the acute analysis. Of note is that the relative contribution from drinking water is minimal. For acute exposures the peak concentration estimated drinking water concentration (EDWC) of 35.6 ppb was directly incorporated into the DEEM_FCID into the food categories "water, direct, all sources" and water, indirect, all sources" (based on a maximum application rate of 3.0 lb ai/A/season for the turf use rate). HED concludes that the acute exposure estimates are unlikely to underestimate actual acute exposure.

The chronic dietary assessment was conducted using tolerance level residues for all crops except for apple, grape, head lettuce, leaf lettuce, celery, spinach, orange, pepper and tomato where average residues from crop field trials were used. These field trials represent maximum application rates and minimum PHIs. Average percent crop treated estimates were used when available from a recent Screening Level Usage Analysis (SLUA). A limited number of experimentally derived processing factors from pyraclostrobin processing studies were also used to refine the analysis. Again, the relative contribution from drinking water is minimal. For chronic exposures the annual average concentration EDWC of 2.3 ppb was directly incorporated into the DEEM_FCID into the food categories "water, direct, all sources" and water, indirect, all sources"(based on a maximum application rate of 3.0 lb ai/A/season for the turf use rate).
HED concludes that the chronic exposure estimates in this analysis are unlikely to underestimate actual exposure.

Acute and chronic exposures and risks do not exceed HED's level of concern for the U.S. population and for all relevant population subgroups. At the 95th percentile, the acute dietary exposure utilized 1.5% of the aPAD for the general U.S. population and 81% of the aPAD for females 13-49 years old, the most highly exposed population subgroup. The chronic dietary exposure utilized 7.3% of the cPAD for the general U.S. population and 24% of the cPAD for children 1-2 years old, the most highly exposed population subgroup.

Aggregate Exposure Assessment

There are existing residential uses on turf which contribute to aggregate exposures. Residential and recreational turf applications are applied by professional pest control operators (PCOs) only, and therefore, residential handler exposures do not occur. There is, however, a potential for exposure to homeowners in residential settings from entering previously treated lawns where children might play and adults might work or play. As a result, risk assessments have been completed for postapplication scenarios. Postapplication short- and intermediate-term dermal and incidental oral exposures are expected to occur from the turf use pattern. Common effects (i.e., decreased body weight gain, food intake, and food efficiency) were seen in the studies selected to evaluate dietary, dermal and incidental oral ingestion exposures; and therefore, route-specific exposures can be aggregated.

Aggregate assessments were conducted for acute and chronic dietary (food + drinking water) exposures. Additionally, short- and intermediate-term aggregate risk assessments were conducted. Both short- and intermediate-term exposures may occur during postapplication activities for adults and children. However, because the toxicity endpoints and points of departure are identical for short- and intermediate-term exposures, separate risk estimates for short- and intermediate-term exposures were not calculated. These short-/intermediate-term aggregate risk assessments take into account average exposure estimates from dietary consumption of pyraclostrobin (food and drinking water) and non-occupational/residential uses (turf), i.e., for toddlers incidental oral, dermal, and average food plus drinking water exposures are aggregated, and for adults, dermal and average food plus drinking water exposures are aggregated.

The total combined MOE from dietary (food + drinking water) and non-occupational/residential exposure is 120 for children 1-2 years old, which is not of concern to HED. For adults the total combined MOE is 230, which also is not of concern to HED. These aggregate exposure risk assessments are considered conservative estimates, that should not underestimate risks, because of the following inputs: 1) dietary inputs primarily used tolerance level residues; 2) crop specific (turf) screening level drinking water modeling data were used (i.e., Tier II surface water model); 3) maximum application rates and minimum application intervals were used; and 4) conservative SOPs and upper level estimates of exposure were employed.

Occupational Handler Exposure Assessment

Agricultural Handler Risk

The proposed supplemental Headline® label requires occupational handlers to wear coveralls and chemical resistant gloves. Occupational exposure and risk resulting in MOEs greater than or equal to 100 are not of concern to HED. All handler scenarios resulted in MOEs greater than the level of concern (MOEs ≥ 100) at some level of risk mitigation. Of note, for the scenario of mixing and loading liquid concentrates to support aerial applications, a dust mist respirator is needed to achieve an MOE ≥ 100, which is not already included on the proposed Headline® label.

Seed Treatment Handler Risk

The proposed supplemental Stamina™ label requires occupational handlers to wear baseline attire (i.e., long-sleeve shirt, long pants, shoes, and socks) and chemical resistant gloves. Most seed treatment activities result in MOEs greater than the LOC of 100 and are not of concern with the proposed personal protective equipment (PPE). However, for the scenario of handlers involved in multiple commercial seed treatment activities ("multiple activities"), a dust mist respirator is needed to achieve an MOE ≥ 100, which is not already included on the proposed Stamina™ label.

Occupational Postapplication Exposure Assessment

Previously submitted chemical-specific dislodgeable foliar residue (DFR) data and the interim transfer coefficient policy developed by HED's Science Advisory Council for Exposure, which includes proprietary data from the Agricultural Reentry Task Force (ARTF) database (policy # 3.1), were used in estimating postapplication exposures following foliar treatment to sorghum. Postapplication risks were not a concern on day 0 (12 hours following application); i.e. MOEs ≥100. Therefore, the restricted entry interval (REI) is based on the acute toxicity of pyraclostrobin technical material which is classified as Category III for acute dermal toxicity and for skin and eye irritation potential. Pyraclostrobin is not a dermal sensitizer. Under the Worker Protection Standard for Agricultural Pesticides, active ingredients classified as acute toxicity categories III or IV for these routes are assigned a 12-hour REI.

Recommendations for Tolerances

HED has completed a human health risk assessment for the proposed new uses of the active ingredient pyraclostrobin.

For Petition #8F7385 - Provided that a revised Section F is submitted reflecting the recommended tolerances and commodity definitions presented in Table 12, the residue chemistry and toxicological databases support the acceptance of a *conditional registration* on sorghum, and establishment of permanent tolerances for the combined residues of pyraclostrobin (carbamic acid, [2-[[[1-(4-chlorophenyl)-1H- pyrazol-3-yl]oxy]methyl]phenyl]methoxy-, methyl ester) and its desmethoxy metabolite (methyl N-[[[1-(4-chlorophenyl)-1H-pyrazol-3-yl]oxy]methyl]phenyl carbamate), expressed as parent compound in/on the following raw agricultural commodities:

Sorghum, grain, forage ....5.0 ppm
Sorghum, grain, grain ....0.60 ppm
Sorghum, grain, stover..0.80 ppm

For Petition #8F7390 - Provided that a revised Section F is submitted reflecting the recommended tolerances and commodity definitions presented in Table 12, the residue chemistry and toxicological databases support the proposed amended use pattern for stone fruit crop group 12 and permanent tolerances for the combined residues of pyraclostrobin (carbamic acid, [2-[[[1-(4-chlorophenyl)-1H- pyrazol-3-yl]oxy]methyl]phenyl]methoxy-, methyl ester) and its desmethoxy metabolite (methyl N-[[[1-(4-chlorophenyl)-1H-pyrazol-3-yl]oxy]methyl]phenyl carbamate), expressed as parent compound in/on the following raw agricultural commodity:

Fruit, stone, group ....2.5 ppm

For Petition #8E7394 – Provided that a revised Section F is submitted, the residue chemistry and toxicological databases support the establishment of a permanent tolerance for the combined residues of pyraclostrobin (carbamic acid, [2-[[[1-(4-chlorophenyl)-1H-pyrazol-3-yl]oxy]methyl]phenyl]methoxy-, methyl ester) and its desmethoxy metabolite (methyl N-[[[1-(4-chlorophenyl)-1H-pyrazol-3-yl]oxy]methyl]phenyl carbamate), expressed as parent compound in/on the following raw agricultural commodity:

Coffee, bean, green ....0.3 ppm

Recommendations for Labels

Stamina™ BAS 500 12 F Label

For the scenario of handlers involved in multiple commercial seed treatment activities ("multiple activities"), a dust mist respirator is needed to achieve an MOE $\geq$ 100, which is not already included on the proposed Stamina™ label.

For the seed treatment uses, the pyraclostrobin seed treatment labeling should be required to add specific statements regarding the personal protective equipment required for persons planting treated seed as well as other label restrictions, as follows:.

- "Seed that has been treated with this product that is then packaged or bagged for future use must contain the following labeling on the outside of the seed package or bag."
- "Treated Seed - Do Not Use for Food, Feed, or Oil Purposes."
- "When opening this bag or loading/pouring the treated seed, wear long-sleeved shirt, long pants, shoes, socks, and chemical resistant gloves."
- "After the seeds have been planted, do not enter or allow worker entry into treated areas during the restricted-entry interval (REI) of 12 hours. Exception: Once the seeds are planted in soil or other planting media, the Worker Protection Standard allows workers to enter the treated area without restriction if there will be no worker contact with the soil/media subsurface."

Headline® Fungicide Label

For the use on sorghum, the scenario of mixing and loading liquid concentrates to support aerial applications, a dust mist respirator is needed to achieve an MOE $\geq$ 100, which is not already included on the proposed Headline® label.

Environmental Justice Considerations

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Review of Human Research

This risk assessment relies in part on data from Pesticide Handlers Exposure Database (PHED) studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies have been determined to require a review of their ethical conduct, have received that review, and have been determined to be ethical.

2.0 Ingredient Profile

2.1 Summary of Registered/Proposed Uses

Pyraclostrobin is currently registered on barley, berries, *Brassica* vegetables, bulb vegetables, canola, citrus, corn (field, pop and sweet), cotton, cucurbit vegetables, flax, fruiting vegetables, grapes, grass grown for seed, hops, leafy vegetables, legumes (dried peas and beans, succulent shelled peas and beans), mint, oats, peanuts, pistachios, pome fruit, potatoes, root vegetables, rye, soybean, strawberries, stone fruits, sugar beets, sunflower, tropical fruits, tuberous and corm vegetables, tree nuts, and wheat, as well as ornamentals, and residential and golf course turf.

A summary of the pyraclostrobin end-use products proposed for use on the crops discussed in this document is listed in Table 1. Table 2 presents the summary of proposed crop use patterns.

TABLE 1. Summary of Proposed Pyraclostrobin End-Use Products.

Trade Name	EPA Reg. No.	% ai of Formulation	Formulation Type	Target Crops	Label Date
Headline® Fungicide	7969-186	23.6%, (2.09 lb ai/gal)	EC	Sorghum	Supplemental label attached in Section B. (June 30, 2008)
Stamina BAS 500 12 F	7969-266	18.4% (1.67 lb ai/gal)	Seed Treatment	Sorghum	Supplemental label attached in Section B. (June 30, 2008)
Pristine® Fungicide BAS 516 04F (Mix with Boscalid)	7969-199	12.8% (1.1 lb ai/gal)	WG	Stone Fruits Group-Apricot, Cherry (sweet and sour), Nectarine, Peach, Plum and Prune.	Label March 27, 2008
Headline® Fungicide (COMET® in Brazil)	7969-186	23.6% (2.09 lb ai/gal)	EC	Coffee	Supplemental label attached in Section B. (June 30, 2008).

TABLE 2. Summary of Proposed Use Patterns of Pyraclostrobin.						
Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Grain Sorghum						
Ground sprayer, aerial, or sprinkler irrigation systems.	[7969-186] 23.6% EC	(0.1-0.2) 6 to 12 fl ozs/A	1	(0.2) 12 fl ozs/A	No later than 25% flowering	Begin applications prior to disease development. Use higher rate (0.15-0.2 lb ai/A) when disease pressure is high (Northern leaf blight and Southern leaf blight). Do not use in greenhouse or transplant production systems. For resistance management, if additional fungicide application is needed use a labeled non-group 11 fungicide with a different mode of action. No aerial application in NY state except as permitted under FIFRA section 24(c).
Grain Sorghum						
Apply as a water-based mixture using standard slurry or mist-type seed treatment application equipment.	[7969-266] 18.4%	(0.001-0.002) 0.01-0.02 lb/100 lbs seed	N/S	N/S	Seed treatment	Use at commercial treatment facilities. Not for use on a farm. Use higher rate when disease pressure is expected to be high. Mechanical agitation is required for proper mixing.
Coffee						
Ground sprayer, aerial, or sprinkler irrigation systems.	[7969-186] 25% EC	(0.1-0.2) 150-200 g/ha	2	N/S	45	Apply when leaf infection indexes up to 5% are observed. Re-apply in dose of 0.1 lb ai/A whenever the infection index by rust reaches up to 5% again. Maximum of two applications.
Stone Fruits Crop Group 12						
Ground application, aerial, or sprinkler irrigation equipment.	[7969-199] 12.8% WG	(0.084-0.117) 10.5-14.5 ozs of product[1]	5	(0.585) 72.5 ozs of product[1]	0	Begin application at pink bud or prior to onset of disease development and continue on a 7-14 day interval. Do not make more than 5 applications of Pristine or other group 7 or 11 fungicides per season. Do not make more than 2 sequential applications before alternating to a labeled fungicide with a different mode of action. For aerial application, use no less than 10 gal of spray solution per acre. Do not apply when wind speed favors drift. Do not use in grrenhouse or transplant production. No aerial application in NY state except as permitted under FIFRA section 24(c).

N/S= not specified

[1] 0.128 oz (0.008lb) of pyraclostrobin in 1 oz of product.

Conclusions. The submitted use directions are sufficient to allow evaluation of the available residue data relative to the proposed use. The field trial data for grain sorghum, the stone fruit crop group 12, and coffee reflect the proposed use patterns.

2.2 Physical and Chemical Properties

The chemical structure of pyraclostrobin and its metabolites are presented in Tables 3 and 4, respectively. Please refer to a previous risk assessment document (DP# 334535, 02/21/08, B. O'Keefe) for a detailed listing of the physical and chemical properties of pyraclostrobin.

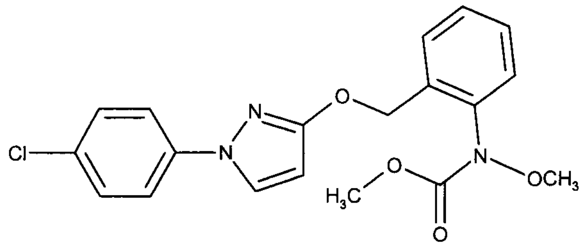
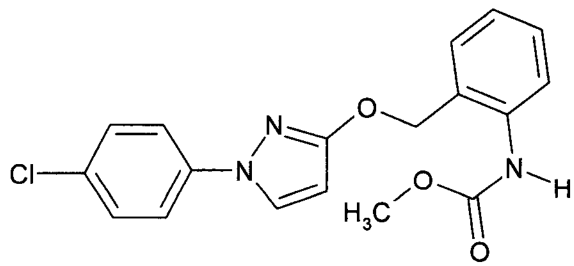
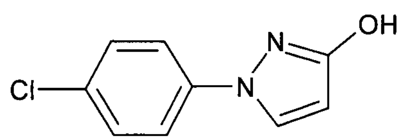
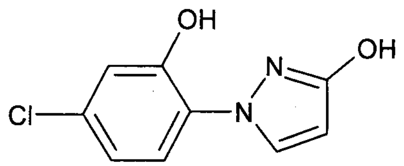
Table 3. Pyraclostrobin Chemical Structure.	
Pyraclostrobin	

Table 4. Chemical Structures of Pyraclostrobin Metabolites.

Metabolites	Structure
BAS 500-3	
BAS 500-5	

Metabolites	Structure
BAS 500-8	

3.0 Hazard Characterization/Assessment

3.1 Hazard Characterization and FQPA Considerations

The quality of the toxicology database for pyraclostrobin is good and the confidence in the hazard and dose-response assessments is high. The toxicity database for pyraclostrobin is considered adequate to support toxicity endpoint selection for risk assessment and for FQPA evaluation. However, under the current 40 CFR §158.500 data requirement guidelines, the immunotoxicity data (OPPTS 780.7800) shall be required as a condition of registration.

To address the issue of immunotoxicity data gap and the associated database uncertainty factor, RAB3 examined the entire database of pyraclostrobin and determined that an additional uncertainty factor is not needed to account for potential immunotoxicity. For pyraclostrobin, a complete battery of subchronic, chronic, carcinogenicity, developmental and reproductive studies as well as acute and subchronic neurotoxicity screening studies are available for consideration. The immunotoxic potential of pyraclostrobin has been well characterized in relationship to other adverse effects seen in the submitted toxicity studies (Memorandum: Yung G. Yang to Cynthia Giles-Parker, 7/24/2007, TXR # 0054636; DP Barcode: D341293). Under the conditions of the studies, the results do not indicate the immune system to be the primary target and, other than the high dose-thymus effects seen in the 90-day mouse study, no significant evidence of pyraclostrobin-induced immunotoxicity was demonstrated either in the studies conducted in adult animals or in the offspring following pre- and post-natal exposures. Currently, the point of departure in establishing the chronic RfD is 3.4 mg/kg/day; the RAB3 risk assessment team does not believe that conducting a special series 870.7800 immunotoxicity study will result in a NOAEL less than 3.4 mg/kg/day. An additional uncertainty factor (UF_{DB}) for database uncertainties does not need to be applied at this time.

A recent pyraclostrobin risk assessment document included an updated toxicology and hazard evaluation, including results of recently submitted toxicity studies, a new carcinogenicity evaluation, and selection of new study/endpoints for exposure by the inhalation route. Please refer to this previous pyraclostrobin risk assessment document for further extensive details (B. O'Keefe, DP Barcode 343700, 9/7/07). Also, please refer to Appendices 2 and 3 of this current risk assessment document for the toxicity profile tables. As there is no new toxicity data associated with these current actions, the hazard characterization and endpoint selection, from the previous risk assessment are applied directly to this action.

Pyraclostrobin has a low to moderate acute toxicity based on its classification in Toxicity Category IV via the oral route, Toxicity Category III by the dermal route, and Toxicity Category II by the inhalation route of exposure. Pyraclostrobin produces moderate eye irritation (Toxicity Category III), is a moderate dermal irritant (Toxicity Category III), and is not a dermal sensitizer (Appendix 2).

The main target organs for pyraclostrobin are the upper gastrointestinal tract (mainly the duodenum and stomach), the spleen/hematopoiesis, and the liver. In the 90-day mouse oral toxicity study, thymus atrophy was seen at doses of 30 mg/kg or above, but similar effect was not found in the mouse carcinogenicity study at doses as high as 33 mg/kg. In reproductive and developmental studies, there was evidence of increased qualitative susceptibility following in utero exposure in the rabbit, but not in rats. In the two-generation reproduction study, the highest dose tested did not cause maternal systemic toxicity, nor did it elicit reproductive or offspring toxicity. Nonetheless, HED determined that, when evaluated with the findings of the dose-range finding one-generation reproduction study (MRID# 45596210), there is no need to repeat the two-generation reproduction study. In both the acute and subchronic neurotoxicity studies, there were no indications of treatment-related neurotoxicity.

The CARC classified pyraclostrobin into the category "Not Likely to be Carcinogenic to Humans" based on no treatment-related increase in tumors in both sexes of rats and mice, which were tested at doses that were adequate to assess carcinogenicity, and the lack of evidence of mutagenicity.

A variety of oral toxicity studies were used for the different risk assessment scenarios including the rabbit developmental toxicity study, the acute neurotoxicity study in rats, the rat carcinogenicity study, and the 13-week study in dogs. In addition, the 28-day inhalation study in rats was used for short- and intermediate-term occupational and residential inhalation risk assessments. The endpoints in these studies are well characterized and are the most sensitive among available comparable toxicity studies in other species. All dietary points of departure (i.e., acute and chronic RfDs) are calculated from the respective study's NOAEL after applying a 100-fold safety factor (10 X to account for interspecies extrapolation and 10X for intraspecies variation). For all other scenarios, including dermal, inhalation, and incidental oral, an MOE approach will be used with a Level of Concern (LOC) at 100.

3.2 FQPA Safety Factor for Infants and Children

Based on the hazard and exposure data, the RAB3 pyraclostrobin risk assessment team concluded that the FQPA safety factor can be reduced to 1X. The recommendation is based on the following:

- The toxicity database is adequate and there are no residual uncertainties for pre- and/or postnatal toxicity. The doses chosen as quantitative risk estimates are adequately protective for infants and children.
- Exposure data are complete or are estimated based on data that reasonably account for potential exposures.

- The acute dietary analysis was based on tolerance level or highest residues and 100% crop treated assumptions for all commodities. Experimentally derived processing factors were used for fruit juices and tomato and wheat commodities. The contribution from drinking water is minimal. HED concludes that the acute exposure estimates in this analysis are unlikely to underestimate actual exposure.

- The chronic dietary analysis included tolerance level or average residues from field trial data and average percent crop treated estimates were used when available from a recent Screening Level Usage Analysis (SLUA). A limited number of experimentally derived processing factors (for fruit juices, tomato and wheat commodities) from pyraclostrobin processing studies were also used to refine the analysis. The field trials represent maximum application rates and minimum PHIs. The contribution from drinking water is minimal. HED concludes that the chronic exposure estimates in this analysis are unlikely to underestimate actual exposure.

- The dietary drinking water assessment utilizes water concentration values generated by model and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations which will not likely be exceeded.

- While there is potential for postapplication residential exposure, the best data and approaches currently available were used in the pyraclostrobin residential assessment. The Agency used the current conservative approaches for residential assessment, many of which include recent upgrades to the SOPs. The Agency believes that the calculated risks represent conservative estimates of exposure because maximum application rates are used to define residue levels upon which the calculations are based. Exposures are unlikely to be under estimated because the assessment was a screening level assessment.

3.3 Summary of Toxicological Doses and Endpoints for Use in Human Health Risk Assessments

HED recently completed a Section 3 human health risk assessment for the use of pyraclostrobin on cotton and Belgian endive (Memo B. O'Keefe, et. al., 9/7/07, DP# 343700). As there is no new toxicity data associated with this current action, the hazard characterization and endpoint selection, from the previous risk assessment are applied directly to this action. All previous exposure risk assessments remain unchanged. Below are the up-to-date tables.

Table 5. Summary of Toxicological Doses and Endpoints for Pyraclostrobin for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population, including Infants and Children)	NOAEL= 300 mg/kg/day	UF_A= 10x UF_H= 10x FQPA SF= 1x	Acute RfD = 3.0 mg/kg/day aPAD = 3.0 mg/kg/day	Rat Acute Oral Neurotoxicity LOAEL = 1000 mg/kg/day based on decreased body weight gain in males.
Acute Dietary (Females 13-49 years of age)	NOAEL = 5.0 mg/kg/day	UF_A= 10x UF_H= 10x FQPA SF= 1x	Acute RfD = 0.05 mg/kg/day aPAD = 0.05 mg/kg/day	Rabbit Prenatal Developmental Toxicity LOAEL = 10.0 mg/kg/day based on developmental toxicity findings of increased resorptions.
Chronic Dietary (All Populations)	NOAEL= 3.4 mg/kg/day	UF_A= 10x UF_H= 10x FQPA SF= 1x	Chronic RfD = 0.034 mg/kg/day cPAD = 0.034 mg/kg/day	Rat Oral Carcinogenicity LOAEL = 9.2 mg/kg/day based on decreased body weight/body weight gain, kidney tubular casts and atrophy in both sexes; increased incidence of liver necrosis and erosion/ulceration of the glandular- stomach and fore-stomach in males.
Incidental Oral Short-Term (1-30 days)	NOAEL= 5.8 mg/kg/day	UF_A= 10x UF_H= 10x FQPA SF= 1x	Residential LOC for MOE = 100	13-Week Feeding Dog Study LOAEL = 12.9 mg/kg/day based on increased incidence of diarrhea, clinical chemistry changes, duodenum mucosal hypertrophy, and decreased body weight and food intake/efficiency.
Incidental Oral Intermediate-Term (1-6 months)	NOAEL= 5.8 mg/kg/day	UF_A= 10x UF_H= 10x FQPA SF= 1x	Residential LOC for MOE = 100	13-Week Feeding Dog Study LOAEL = 12.9 mg/kg/day based on increased incidence of diarrhea, clinical chemistry changes, duodenum mucosal hypertrophy, and decreased body weight and food intake/efficiency.
Dermal Short-Term (1-30 days)	Oral study NOAEL = 5.0 mg/kg/day (dermal absorption rate = 14 %)	UF_A= 10x UF_H= 10x FQPA SF= 1x	Residential LOC for MOE = 100	Rabbit Prenatal Developmental Toxicity LOAEL = 10.0 mg/kg/day based on developmental toxicity findings of increased resorptions and maternal toxicity based on decreased body weight gain and decreased food intake/efficiency.

Table 5. Summary of Toxicological Doses and Endpoints for Pyraclostrobin for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Intermediate-Term (1-6 months)	Oral study NOAEL = 5.0 mg/kg/day (dermal absorption rate = 14 %)	UF_A= 10x UF_H= 10x FQPA SF= 1x	Residential LOC for MOE = 100	Rabbit Prenatal Developmental Toxicity LOAEL = 10.0 mg/kg/day based on developmental toxicity findings of increased resorptions and maternal toxicity based on decreased body weight gain and decreased food intake/efficiency.
Long-Term Dermal (>6 months)	Oral study NOAEL = 3.4 mg/kg/day (dermal absorption rate = 14 %)	UF_A= 10x UF_H= 10x FQPA SF= 1x	Residential LOC for MOE = 100	Rat Oral Carcinogenicity LOAEL = 9.2 mg/kg/day based on decreased body weight/body weight gain, kidney tubular casts and atrophy in both sexes; increased incidence of liver necrosis and erosion/ulceration of the glandular- stomach and fore-stomach in males.
Inhalation Short-Term (1-30 days)	NOAEL= 0.23 mg/kg/day (air concentration = 0.001 mg/L)	UF_A= 10x UF_H= 10x FQPA SF= 1x	Residential LOC for MOE = 100	Rat 28-day Inhalation LOAEL = 6.9 mg/kg/day (air concentration = 0.03 mg/L) based on duodenum mucosal hyperplasia and respiratory system findings including alveolar histiocytosis and olfactory atrophy/necrosis in nasal tissue.
Inhalation Intermediate-Term (1-6 months)	NOAEL= 0.23 mg/kg/day (air concentration = 0.001 mg/L)	UF_A= 10x UF_H= 10x FQPA SF= 1x	Residential LOC for MOE = 100	Rat 28-day Inhalation LOAEL = 6.9 mg/kg/day (air concentration = 0.03 mg/L) based on duodenum mucosal hyperplasia and respiratory system findings including alveolar histiocytosis and olfactory atrophy/necrosis in nasal tissue.
Inhalation Long-Term (>6 months)	NOAEL= 0.23 mg/kg/day (air concentration = 0.001 mg/L)	UF_A= 10x UF_H= 10x FQPA SF= 1x	Residential LOC for MOE = 100	Rat 28-day Inhalation LOAEL = 6.9 mg/kg/day (air concentration = 0.03 mg/L) based on duodenum mucosal hyperplasia and respiratory system findings including alveolar histiocytosis and olfactory atrophy/necrosis in nasal tissue.
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans" based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key date (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 6. Summary of Toxicological Doses and Endpoints for Pyraclostrobin for Use in Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short-Term (1-30 days)	NOAEL= 5.0 mg/kg/day (dermal absorption rate = 14 %)	UF_A=10x UF_H=10x	Occupational LOC for MOE = 100	Rabbit Prenatal Developmental Toxicity LOAEL = 10.0 mg/kg/day based on developmental toxicity findings of increased resorptions.
Dermal Intermediate-Term (1-6 months)	Oral study NOAEL = 5.0 mg/kg/day (dermal absorption rate = 14 %)	UF_A= 10x UF_H= 10x	Occupational LOC for MOE = 100	Rabbit Prenatal Developmental Toxicity LOAEL = 10.0 mg/kg/day based on developmental toxicity findings of increased resorptions.
Long-Term Dermal (>6 months)	Oral study NOAEL = 3.4 mg/kg/day (dermal absorption rate = 14 %)	UF_A= 10x UF_H= 10x	Occupational LOC for MOE = 100	Rat Oral Carcinogenicity LOAEL = 9.2 mg/kg/day based on decreased body weight/body weight gain, kidney tubular casts and atrophy in both sexes; increased incidence of liver necrosis and erosion/ulceration of the glandular- stomach and fore-stomach in males.
Inhalation Short-Term (1-30 days)	NOAEL= 0.23 mg/kg/day (air concentration = 0.001 mg/L)	UF_A= 10x UF_H= 10x	Occupational LOC for MOE = 100	Rat 28-day Inhalation LOAEL = 6.9 mg/kg/day (air concentration = 0.03 mg/L) based on duodenum mucosal hyperplasia and respiratory system findings including alveolar histiocytosis and olfactory atrophy/necrosis in nasal tissue.
Inhalation Intermediate-Term (1-6 months)	NOAEL= 0.23 mg/kg/day (air concentration = 0.001 mg/L)	UF_A= 10x UF_H= 10x	Occupational LOC for MOE = 100	Rat 28-day Inhalation LOAEL = 6.9 mg/kg/day (air concentration = 0.03 mg/L) based on duodenum mucosal hyperplasia and respiratory system findings including alveolar histiocytosis and olfactory atrophy/necrosis in nasal tissue.
Inhalation Long-Term (>6 months)	NOAEL= 0.23 mg/kg/day (air concentration = 0.001 mg/L)	UF_A= 10x UF_H= 10x	Occupational LOC for MOE = 100	Rat 28-day Inhalation LOAEL = 6.9 mg/kg/day (air concentration = 0.03 mg/L) based on duodenum mucosal hyperplasia and respiratory system findings including alveolar histiocytosis and olfactory atrophy/necrosis in nasal tissue.
Cancer (oral)	Classification: "Not likely to be Carcinogenic to Humans" based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key date (i.e., lack of a critical study). MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

3.4 Recommendation for Aggregate Exposure Risk Assessments

As per the FQPA, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. When common toxicity endpoints are selected for these routes of exposure they may be aggregated. Aggregate assessments are required for acute and chronic dietary (food + water) exposures, and short-term residential exposures (i.e., chronic dietary plus incidental oral and dermal exposures).

Residential short-/intermediate-term dermal exposure for adults and toddlers were assessed using the NOAEL (5 mg/kg/day) from the rabbit developmental study. While the developmental effect of increased resorptions is not applicable to toddlers, it should be noted that the maternal NOAEL from this study is also 5 mg/kg/day, and is based on reduced body weight gain, food consumption, and food efficiency at the LOAEL of 10 mg/kg/day; this more relevant endpoint was used to assess toddler dermal exposure. For incidental oral ingestion, exposure was assessed using the endpoint from a 13-week feeding study in the dog. The NOAEL from this study is 5.8 mg/kg/day, based on increased incidence of diarrhea, clinical chemistry changes, duodenum mucosal hypertrophy, and decreased body weight and food intake/efficiency at the LOAEL of 12.9 mg/kg/day. A common effect (i.e., decreased body weight gain, food intake, and food efficiency) was seen in the studies selected to evaluate toddler dermal and incidental oral ingestion exposure; therefore, route-specific MOEs were aggregated for toddlers.

3.5 Endocrine disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, pyraclostrobin may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

4.0 Public Health and Pesticide Epidemiology Data

The Centers for Disease Control (CDC) and Prevention recently reported and described five incident events to the Iowa Department of Public Health (IDPH) of exposures that occurred during aerial applications of pyraclostrobin (MMWR Weekly, 2/4/08, 56(51) pp.1343-1345). IDPH investigated the reports. In one event migrant workers were inadvertently exposed to pyraclostrobin due to pilot error and off-target drift of pyraclostrobin to an adjacent field. The migrant workers experienced symptoms including upper respiratory tract pain or irritation, chest pain, nausea, skin redness, eye pain, weakness, headache, and dizziness. In another event, a crop-dusting pilot suffered first degree burns after being exposed to pyraclostrobin which had spilled after his airplane crashed during takeoff. Another three events also involved acute pesticide poisoning associated with off-target drift of pyraclostrobin from nearby aerial applications. In all five of these cases, symptoms subsided after the exposed persons moved indoors or away from the pyraclostrobin treated fields.

Pyraclostrobin labels that permit aerial applications contain specific label language stating not to apply under circumstances where possible drift may occur and how to reduce drift potential.

5.0 Dietary Exposure/Risk Characterization

Reference: *Pyraclostrobin: Petitions for the Establishment of Permanent Tolerances on Grain, Sorghum Grain, Forage and Stover (PP#8F7385); Increase of Tolerance for the Stone Fruit Crop Group 12 to satisfy European Union (EU) import requirement (PP#8F7390); and Establishment of a Permanent import Tolerance for Coffee (PP#8E7394). Summary of Analytical Chemistry and Residue Data. DP359194; M. Negussie; 04/02/09.*

5.1 Pesticide Metabolism and Environmental Degradation

5.1.1 Metabolism in Primary Crops

Adequate metabolism studies with pyraclostrobin on grapes, potatoes, and wheat have previously been reviewed (D269668, L. Cheng, 11/28/01) in conjunction with PP#0F06139. The results of these studies indicate that the metabolism of pyraclostrobin is similar in the three crops investigated. The HED Metabolism Assessment Review Committee (MARC) concluded that the nature of the residue in plants is understood (HED Metabolism Committee Decision Memo; D278044, L. Cheng, 10/9/01). For purposes of tolerance setting and risk assessment, the terminal residues of concern in plants consist of pyraclostrobin and its desmethoxy metabolite (BF 500-3).

5.1.2 Metabolism in Livestock

Adequate metabolism studies with pyraclostrobin on ruminants and laying hens were previously reviewed (D269668, L. Cheng, 11/28/01) in conjunction with PP#0F06139. The HED MARC has determined that for purposes of tolerance setting and risk assessment, the residues of concern in livestock commodities consist of pyraclostrobin and its metabolites convertible to 1-(4-chlorophenyl)-1*H*-pyrazol-3-ol and 1-(4-chloro-2-hydroxyphenyl)-1*H*-pyrazol-3-ol (BF 550-5) (HED Metabolism Committee Decision Memo; D278044, L. Cheng, 10/9/01).

5.1.3 Analytical Methodology

Enforcement Method for Plants

Two adequate methods were proposed for enforcing tolerance for residues of pyraclostrobin and BF 500-3 in/on plant commodities: a LC/MS/MS method (BASF Method D9808), and an HPLC/UV method (BASF Method D9904). The validated method LOQ for both pyraclostrobin and BF 500-3 is 0.02 ppm in all tested plant matrices, for a combined LOQ of 0.04 ppm. Adequate independent method validation and radiovalidation data were submitted for both methods (D269668, 11/28/01, L. Cheng). Following the SOP (ACB-019) for reviewing tolerance methods (September 15, 2008), HED has determined that Method D9904 is suitable as an enforcement method.

Except for green coffee beans, samples of raw agricultural and processed commodities from the current crop field trials (PP#8F7385, PP#8F7390 and PP#8E7394) were analyzed for residues of pyraclostrobin and BF 500-3 using the LC/MS/MS method (BASF Method D9908, version II for sorghum). Briefly, residues were extracted by shaking with methanol:water:2 N HCl (70:25:5; v:v:v), methanol:water (70:30, v:v) and centrifuged. Residues were then partitioned with cyclohexane and 1N HCL saturated with NaCl, concentrated to dryness, and re-dissolved in buffered methanol:water (80:20, v:v). The final chromatographic analysis of residues was determined by LC/MS/MS. Total residues of pyraclostrobin and BF 500-3 are expressed as pyraclostrobin equivalents. For each analyte, the validated method LOQ is 0.02 ppm. The method is adequate for data collection based on acceptable concurrent method recovery data.

Samples of coffee (green beans) (PP#8E7394) in Brazil were analyzed for residues of pyraclostrobin and its metabolite BF 500-3 using an LC/MS/MS method according to SOP-PA.0243 based on BASF method 445/0. Sample extraction is similar to Method D9908 described above, except the final extract is re-dissolved in buffered methanol:water (50:50, v:v). For each analyte, the validated method LOQ is 0.02 ppm, and the calculated LODs are 0.003 ppm for pyraclostrobin and 0.001 ppm for BF-500-3. The method is adequate for data collection based on acceptable concurrent method recovery data.

Analytical Methods - Livestock

In a previous petition (PP#0F06139), two methods were proposed for enforcing tolerances for livestock commodities: HPLC/UV method 439/0 and Method 446 (consisting of GC/MS method 446/0 and LC/MS/MS method 446/1). The HPLC/UV method determines residues of pyraclostrobin *per se*. Method 446 has a hydrolysis step, and determines residues of pyraclostrobin and its metabolites as BF 500-5 and BF 500-8. The validated method LOQs for BF 500-5 type residues, in parent equivalents, are 0.01 ppm for milk and 0.05 ppm for tissues, and the validated LOQs for BF 500-8 type residues, in parent equivalents, are 0.01 ppm for milk and 0.05 ppm for tissues. Independent method validation data for the HPLC/UV and LC/MS/MS methods are acceptable (D269668, 11/28/01, L. Cheng). Radiovalidation data submitted for the GC/MS and LC/MS/MS methods are adequate for liver and milk, and marginal for muscle. Following the SOP (ACB-019) for reviewing tolerance methods (September 15, 2008), HED has determined that Method 446 is suitable as an enforcement method. An enforcement method for poultry was reviewed in PP#0F06139. However, tolerances for poultry egg and tissues have not been established and are not required for the purpose of these petitions.

Multiresidue Methodology (860.1360)

Data pertaining to the multiresidue methods testing of pyraclostrobin and its desmethoxy metabolite were previously reviewed (PP#0F6139, D269668, 11/28/01, L. Cheng). Pyraclostrobin was successfully evaluated through several of the FDA protocols, while recovery of BF 500-3 was unsuccessful in all protocols. Pyraclostrobin was completely recovered through Protocol D (in grape) and E (in grape), and partially recovered through Protocol F (in peanut). Metabolite BF 500-3 had poor peak shape and inadequate sensitivity with Protocol C columns, and therefore, was not further analyzed under Protocol D, E, and F. The results of the multiresidue testing for pyraclostrobin were forwarded to FDA on 1/4/02 for the purpose of updating PAM, Volume I.

5.1.4 Storage Stability Data

Adequate storage stability studies are available indicating that pyraclostrobin and metabolite BF 500-3 are relatively stable at ≤-10°C in fortified samples of grape juice (juices), sugar beet tops (leafy vegetables), sugar beet roots (root crop), tomato (fruit/fruiting vegetable), wheat grain (non-oily grain) and wheat straw (dry feed) for up to 25 months, and in fortified samples of peanut nutmeats (oilseed) and peanut oil for up to 19 months (D269668, L. Cheng, 11/28/01).

Conclusions. There are adequate storage stability data from PP#0F6139 which may be translated in the current petitions to validate sample storage conditions and durations. There are no corrections which need to be applied as pyraclostrobin residues of concern were found to be relatively stable over a wide range of commodities under frozen storage conditions for 19-25 months.

5.1.5 Magnitude of the Residue in Plants

BASF has submitted grain sorghum field trials supporting a new use of pyraclostrobin (EC) and seed treatment on grain sorghum, along with an increased tolerance petition on stone fruits. In addition, BASF has submitted coffee field trials plus a processing study on coffee to support a tolerance on imported coffee. The results from these studies are summarized and discussed below.

Stone Fruit Crop Group – DER Reference: 47470201.der

BASF Corporation submitted adequate field trial residue data reflecting the maximum proposed use pattern of pyraclostrobin on stone fruits (cherries (sweet and sour), peaches, and plums). A summary of the residue data from the field trials is presented in Table . The combined residues of pyraclostrobin and its metabolite BF 500-3 did not exceed the proposed tolerance level of 2.5 ppm in/on stone fruits following five applications of the 2.0 lb/gal EC formulation of pyraclostrobin reflecting a PHI of 0-days. Samples were analyzed using an adequate analytical method, and are supported by the available storage stability data. The number and locations of field trials are in accordance with OPPTS Guideline 860.1500, and the conducted field trials reflect the maximum proposed foliar use pattern.

TABLE 7. Summary of Residues from the Crop Field Trials – Pyraclostrobin & its Desmethoxy Metabolite.

Crop Matrix	Total Applic. Rate (lb ai/A)	PHI (days)	Residues (mg/kg)				
			Mean	Std. Dev.	HAFT	Min.	Max.
Stone Fruit (proposed use = 0.585 lb ai/A total application rate, 0-day PHI)							
Sweet Cherry	0.585	0	0.764	0.624	1.605	0.04	1.88
Sour Cherry	0.585	0	0.955	0.320	1.165	0.52	1.33
Peach	0.585	0	0.602	0.493	1.645	0.31	1.75
Plum	0.585	0	0.198	0.159	0.395	0.04	0.45

The field trial data for all stone fruits (cherry, peach, and plum) reflecting the 0.585 lb ai/A were entered into the Agency's tolerance spreadsheet as specified by the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP to determine an appropriate tolerance level. The tolerance spreadsheet recommends a tolerance of 2.5 ppm for stone fruits crop group 12.

Grain Sorghum – DER Reference: 47470203.der

BASF Corporation submitted adequate field trial residue data reflecting the maximum proposed use pattern (foliar and seed treatment) of pyraclostrobin on grain sorghum. A summary of the residue data from the field trials is presented in Table 8. The combined residues of pyraclostrobin and its metabolite BF 500-3 did not exceed the proposed tolerance level of 5.0 ppm and 0.5 ppm in/on sorghum forage and grain, respectively. However, in sorghum stover, the combined residue value was slightly higher (0.85) than the proposed value of 0.80 ppm. Samples were analyzed using adequate methods and are supported by the available storage stability data.

TABLE 8. Summary of Residues from the Crop Field Trials – Pyraclostrobin & its Desmethoxy Metabolite.

Crop Matrix	Total Applic. Rate (lb ai/A)	PHI (days)	Residues (ppm)				
			Mean	Std. Dev.	HAFT	Min.	Max.
Sorghum Grain (proposed use = 0.20 lb ai/A total application rate, 13-122-day PHI)							
Sorghum forage	0.20	13-43	0.61	0.52	1.72	<0.04	1.96
Sorghum grain	0.20	46-122	0.09	0.11	0.41	<0.04	0.47
Sorghum stover	0.20	46-122	0.17	0.21	0.75	<0.04	0.85

The field trial data for grain sorghum (forage, grain, and stover) reflecting the 0.19 - 0.22 lb ai/A application rate were entered into the Agency's tolerance spreadsheet as specified by the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP to determine an appropriate tolerance level. The tolerance spreadsheet recommends a tolerance of 5.0 ppm for sorghum forage, 0.60 ppm for sorghum grain, and 0.80 ppm for sorghum stover.

Coffee – DER Reference: 47470204

BASF Corporation submitted adequate field trial residue data reflecting the maximum proposed use pattern of pyraclostrobin on coffee beans. A summary of the residue data from the field trials is presented in Table 9. The combined residues of pyraclostrobin and its metabolite BF 500-3 did not exceed the proposed tolerance level of 0.5 ppm in/on coffee beans harvested 44 days after the last application, following two foliar applications of an EC formulation at ~0.178 lb ai/A/application and 0.134 lb ai/A for a total seasonal application rate of ~0.312 lb ai/A. The combined residues were 0.04 - 0.15 mg/kg. Samples were analyzed using adequate methods and are supported by the available storage stability data.

TABLE 9. Summary of Residues from the Crop Field Trials– Pyraclostrobin & its Desmethoxy Metabolite

Crop Matrix	Total Applic. Rate (lb ai/A)	PHI (days)	Residues (ppm)				
			Mean	Std. Dev.	HAFT[1]	Min.	Max.
Coffee (total application rate-not specified, 45-day PHI)							
Coffee	0.312	45	0.064	0.048	--	0.04	0.15

1 = Only one sample collected per field trial.

The field trial data for coffee reflecting 0.312 lb ai/A were entered into the Agency's tolerance spreadsheet as specified by the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP to determine an appropriate tolerance level. The tolerance spreadsheet recommends a tolerance of 0.30 ppm for coffee, which is slightly lower than the level (0.5 ppm) proposed by the petitioner.

5.1.6 Magnitude of the Residue in Processed Food/Feed

Coffee – DER Reference: 47470202

In conjunction with the coffee field trials, BASF Corporation submitted a processing study for pyraclostrobin on coffee. Two field trials were conducted in Costa Rica during the 2007 growing season. The treated plots received two broadcast foliar applications of the EC at 0.82 - 0.89 lb ai/A (918 - 996 g ai/ha) (~5X the proposed rate) and 0.68 lb ai/A (758 - 760 g ai/ha) (~5X the proposed rate) for a total rate of 1.50 - 1.57 lb ai/A (1.678 - 1.754 kg ai/ha/season). There was a 61-day retreatment interval between the applications, which were made 105 and 44 days before harvest. Treated samples of mature coffee were harvested 44 days after the last application. Green coffee beans were processed to cleaned green bean, roasted bean, coffee extract, dried spent grounds, liquor extract and freeze-dried instant coffee using simulated commercial procedures. Storage stability data are not required since the samples were stored less than 30 days from collection to analysis. However, adequate storage stability data are available to support storage conditions and durations of samples.

A summary of residue data from the coffee processing study is presented in Table 10. A comparison of the residues in the RAC with those in each processed fraction indicated that residues of pyraclostrobin do not concentrate in coffee processed fractions.

TABLE 10. Residue Data from Coffee Processing Study– Pyraclostrobin & its Desmethoxy Metabolite.

RAC; Trial ID	Processed Commodity	Total Rate (lb ai/A)	PHI (days)	Combined Residues of Pyraclostrobin and its BF 500-3 Metabolite (ppm)			Processing Factor
				Pyraclostrobin	BF-500-3	Combined	
Green beans (RAC); RCN R070040	Green beans (RAC)	1.57	44	0.0984; 0.0997	<0.0259; 0.0237	<0.12; <0.12	N/A; N/A
	Cleaned green bean			0.0881; 0.0868	<0.02; <0.02	<0.11; <0.11	0.9; 0.9
	Roasted beans			<0.02; <0.02	<0.02; <0.02	<0.04; <0.04	0.2; 0.2
Green beans (RAC); RCN R070040	Dried spent grounds			<0.02; <0.02	0.0238; 0.0204	<0.04; <0.04	0.2; 0.2
	Liquor extract			<0.02; <0.02	<0.02; <0.02	<0.04; <0.04	0.2; 0.2
	Instant coffee			<0.02; <0.02	<0.02; <0.02	<0.04; <0.04	0.2; 0.2
Green beans (RAC); RCN R070041	Green beans (RAC)	1.50	44	0.0333; 0.0368	<0.02<0.02;	<0.05; <0.06	N/A; N/A
	Cleaned green bean			0.0350; 0.0343	<0.02<0.02;	<0.06; <0.05	1.1X; 0.9
	Roasted beans			<0.02; <0.02	<0.02<0.02;	<0.04; <0.04	0.6; 0.5
Green beans (RAC); RCN R070041	Dried spent grounds			<0.02; <0.02	<0.02<0.02;	<0.04; <0.04	0.6; 0.5
	Liquor extract			<0.02; <0.02	<0.02<0.02;	<0.04; <0.04	0.6; 0.5
	Instant coffee			<0.02; <0.02	<0.02<0.02;	<0.04; <0.04	0.6; 0.5

Conclusions. The coffee processing study is adequate. Residues of pyraclostrobin were detected in the green bean RAC and cleaned green bean from a field trial treated at an exaggerated 5x rate. Combined residues were non-quantifiable in all other coffee processed fractions, with the exception of two treated dried spent grounds samples from one of the trials (RCN R070040) that contained combined residues at 0.04 ppm. The data indicate that residues of pyraclostrobin and its metabolite do not concentrate in cleaned green bean, coffee roasted beans, dried spent grounds, liquor extract, and instant coffee samples.

Stone Fruits – Residue Chemistry Memo, DP# 269668, 11/28/01, L. Cheng (PP#0F6139)

Field trial data was previously submitted (PP#0F6139) depicting the potential for concentration of residues of pyraclostrobin in prunes, the only processed commodity of plums. The submitted plum processing data were adequate. The data indicate that the combined residues of pyraclostrobin and its metabolite BF 500-3 concentrated slightly in prunes at 1.2x and 1.3x.

Conclusions. The HAFT residue of plums treated at 1x the maximum seasonal rate (0.6 lb ai/A/season; 0-day PHI) from the submitted plum field trial studies was 0.19 ppm for pyraclostrobin and <0.02 ppm for BF 500-3 (<0.21 ppm combined residues). Based on the HAFT (<0.21 ppm) and an average concentration factor of 1.3x, the maximum expected pyraclostrobin and BF 500-3 residues in prunes would be 0.273 ppm, which is lower than the proposed RAC tolerance of 2.5 ppm for the stone fruits crop group. Based on these data, a tolerance for pyraclostrobin residues in prunes is not warranted.

5.1.7 Magnitude of the Residue in Meat, Milk, Poultry, and Eggs

Livestock dietary burdens

No new livestock feeding studies were submitted with these petitions. The potential for transfer of pyraclostrobin residues of concern to meat, milk, poultry, and eggs exists because there are several livestock feedstuffs (sorghum forage, sorghum grain, and sorghum forage) that are associated with the proposed use in the current petition (PP#8F7385). The livestock dietary burdens of pyraclostrobin are presented in Table 11, and reflect the most recent guidance from HED concerning revisions of feedstuff percentages in OPPTS 860.1000 Table 1 and construction of reasonably balanced livestock diets (RBLDs). The new livestock feedstuffs included in the current petition are sorghum grain, sorghum forage, and sorghum stover. The calculated dietary burdens of pyraclostrobin are estimated at 4.9 ppm (beef), 9.5 ppm (dairy), 0.95 ppm (poultry), and 0.55 ppm (swine). The current dietary burdens for cattle and poultry differ very slightly from the previous estimates (D343754, J. Stokes, 2/12/2008).

Table 11. Calculation of Reasonably Balanced Dietary Burdens (RBDBs) of Pyraclostrobin Residues for Livestock. [1]

Feedstuff	Type	% Dry Matter	% Diet	Tolerance (ppm)	Dietary Contribution (ppm)
Beef Cattle R 15%, CC 80%, PC 5%					
Barley, hay	R	88	10	25	2.84
Cotton, gin byproducts	R	90	5	30	1.67
Barley, grain	CC	88	20	0.4	0.091
Corn, field, grain/milled byproducts	CC	88	20	0.1	0.023
Canola/sunflower, meal	PC	92	5	0.3	0.016
Sorghum, grain, forage/silage	R	35	--	5.0	--
Sorghum, grain, grain	CC	86	40	0.6	0.27
Sorghum, grain, stover	R	88	--	0.8	--
TOTAL BURDEN	--	--	100		**4.9**
Dairy Cattle R 45%, CC 45%, PC 10%					
Almond, hulls	R	90	5	1.6	0.09
Legume, hay (cowpea)	R	30	5	25	4.16
Barley, grain	CC	88	20	0.4	0.091
Cotton, undelinted seed	PC	90	10	0.3	0.033
Sorghum, grain, forage/silage	R	35	35	5.0	5
Sorghum, grain, grain	CC	86	25	0.6	0.15
Sorghum, grain, stover	R	88	--	0.8	--
TOTAL BURDEN	--	--	100	--	**9.5**
Poultry CC 75%, PC 25%					
Oat, grain	CC	88	70	1.2	0.84
Canola/sunflower, meal	PC	92	25	0.3	0.075
Sorghum, grain, grain	CC	86	5	0.6	0.03
TOTAL BURDEN	--	--	100	--	**0.945**
Swine CC 85%, PC 15%					
Barley, grain	CC	88	5	0.4	0.02
Canola/sunflower, meal	PC	92	15	0.3	0.045
Sorghum, grain, grain	CC	86	80	0.6	0.48
TOTAL BURDEN	--	--	100	--	**0.545**

[1] All data are based on Table 1 Feedstuffs (June 2008), a revision of feedstuffs data found in Table 1 (180.1000 OPPTS Test Guidelines). Residue levels for beef and dairy are corrected for moisture content and are determined by formula: tolerance / %DM x % in diet. Residue levels for poultry and swine are considered "as-is" and are determined by formula: tolerance x % in diet. R: roughage; CC: carbohydrate concentrate; PC: protein concentrate.

Typical compositions of daily rations for the animals of choice for Table 1 data follow:

Feedlot beef are fed higher amounts of CC (up to 80 %), and lower amounts of R (15-20 %) and PC (5-10 %) as the slaughter time (last 3 months) gets closer. High volume milk-producing lactating dairy cows have a daily ration of 45 % R, 40-45 % CC, and 10-15 % PC.
A laying hen that will give a steady egg production is fed 75-80 % CC and 20-25 % PC. A marketable hog diet that will give steady growth would have 80-85 % CC and 15-20 % PC.

Livestock feeding studies: Residue Chemistry Memo, DP# 269668, 11/28/01, L. Cheng (PP#0F6139)

Adequate feeding studies were reviewed in PP#0F6139. The current pyraclostrobin tolerances for livestock commodities were established based on results from these studies and the Agency's estimated dietary burdens for pyraclostrobin residues, which were originally calculated to be 36.3 ppm for beef cattle, 35.4 ppm for dairy cattle, and 0.35 ppm for poultry. The more recent dietary burden for pyraclostrobin residues are estimated at 4.9 ppm (beef), 9.5 ppm (dairy), 0.95 ppm (poultry), and 0.55 ppm (swine). In the poultry feeding study, laying hens were orally dosed once daily for 30 consecutive days with pyraclostrobin at dose levels equivalent to 0.28 ppm (0.3x), 0.88 ppm (0.9x), and 3.01 ppm (3.0x). At the highest feeding level of 3.01 ppm, residues of pyraclostrobin and its metabolites hydrolyzable to BF 500-5 were less than the method LOQ (0.05 ppm) in all egg and tissue samples, except for one egg sample (Day 17) where residues of pyraclostrobin were detected at 0.064 ppm and <0.05 ppm upon re-analysis. Residue analysis of BF 500-8 was not conducted (the metabolism data show all metabolites hydrolyzable to BF 500-8 would be less than 10% TRR), but instead an isomeric compound (BF 500-9) was measured. Levels of BF 500-9 also were all <0.05 ppm.

Conclusions: Based on these dietary exposure levels and the residue data from the ruminant feeding study, the existing pyraclostrobin tolerances for milk (0.1 ppm), meat (0.1 ppm), fat (0.1 ppm), meat byproducts except liver (0.2 ppm), and liver (1.5 ppm) of cattle, goats, hogs, horses, and sheep are adequate to support the proposed uses. Tolerances for eggs and poultry are not needed based on data from the poultry feeding and metabolism studies [Category 180.6(a)(3)]. If, in the future, the petitioner proposes a use which increases the dietary burdens of poultry, then the Category 3 situation will be re-evaluated.

5.1.8 Confined and Field Rotational Accumulation in Rotational Crops

An adequate confined rotational crop study is available on pyraclostrobin (PP#0F6139, D269668, L. Cheng, 11/28/01; D314519, L. Cheng, 05/05/05). The confined study indicates that the metabolism of pyraclostrobin in rotated crops is similar but more extensive than that in primary crops. Pyraclostrobin undergoes demethoxylation to yield BF 500-3, followed by further degradation to medium polar and polar metabolites, and subsequent conjugation reactions and incorporation into natural products. The MARC (D278044, L. Cheng, 10/09/01) concluded that the residues of concern in rotational crops consist of pyraclostrobin and metabolite BF 500-3.

An adequate limited field rotational crop study is available (PP#0F6139, D269668, L. Cheng, 11/28/01) reflecting six broadcast foliar applications of pyraclostrobin (EC) to cucumber at 0.19-0.20 lb ai/A/application and RTIs of 6-8 days, for a total of 1.2 lb ai/A/season. This rate is 1x the maximum use rate of any rotated crop. Average residues of pyraclostrobin and BF 500-3 were each <LOQ in/on RAC samples from all representative rotational crops (radish, cabbage and wheat) planted 14 days following the final application to the primary crop. These data indicate that the label specified 14-day

plant-back restriction is acceptable for all crops that are not registered for direction application.

5.1.9 Drinking Water Residue Profile

References: *Drinking Water Exposure Assessment for the Section 3 New Use Registration of Pyraclostrobin on Sorghum; DP Barcode 356965; R. Miller; 12/17/08*

"Tier II Drinking Water Assessment for the use of Pyraclostrobin (P.C. Code: 099100) on Oats and Oilseed (canola and flax) (Headline Fungcide); Corn, Soybean, and Sugar beets (Headline Fungcide); Fresh Herbs (crop group 19) and Tropical Fruits (avocado, black sapote, canistel, mamey sapote, mango, papaya, sapodilla, and star apple) (Pristine Fungicide); and Turf and Ornamentals (Insignia Fungicide) (DP Barcodes 336190, 340588, 342584). G. Rothman, 9/6/07"

The Environmental Fate and Effects Division (EFED) reviewed the proposed use rates associated with the Section 3 request for the use of pyraclostrobin on sorghum. EFED's assessment was based on the application of the highest seasonal use rate (proposed or registered) of pyraclostrobin. The existing registered use of aerial application on turf and ornamentals contains the highest application rate at 0.5 lbs a.i./acre with 6 maximum seasonal applications at 14 day intervals. EFED believes that the aerial use of pyraclostrobin on turf and ornamentals will pose the upper-bound concentrations in surface and ground water since spray drift increases and application efficiency decreases in an aerial application technique.

Measures of exposure for pyraclostrobin in the drinking water assessment were obtained through modeling efforts only, since national-scale monitoring data were not identified. The Tier II drinking water assessment was performed using the Tier II PRZM/EXAMS (PE4V01 perl shell with PRZM 3.12 beta dated 5/24/01 and EXAMS version 2.98, 7/18/02) to assess surface water. Ground water concentrations were estimated using a Tier I SCI-GROW model (version 2.3, May 16, 2006) since a Tier II model has not been developed to assess ground water.

Acute effects of pyraclostrobin residues in drinking water are expressed in annual peak one-in-ten year concentrations, chronic effects in annual average one-in-ten year concentrations, and cancer effects in 30-year average concentrations. The upper-bound Tier II modeling predicts that the estimated drinking water concentrations (EDWCs) of pyraclostrobin in surface water are not likely to exceed 35.6 µg/L for the peak concentration, 2.3 µg/L for the annual average concentration, and 1.5 µg/L for the 30-year average concentration. The SCI-GROW model predicts the acute and chronic EDWCs of pyraclostrobin in shallow ground water to be 0.02 µg /L (0.02 ppb).

5.1.10 Proposed Tolerances

For purposes of both the tolerance expression and dietary risk assessment, HED has concluded that the residues of concern in plant commodities include pyraclostrobin and its desmethoxy metabolite, BF 500-3 (D278044, L. Cheng, 10/9/01), and the residues of concern in livestock commodities include pyraclostrobin and its metabolites convertible to 1-(4-chlorophenyl)-1H-pyrazol-3-ol (BF 500-5) and 1-(4-chloro-2-hydroxyphenyl)-1H-pyrazol-3-ol (BF 500-8).

Pyraclostrobin tolerances for plant commodities are listed in 40 CFR §180.582 (a)(1) and are expressed in terms of the combined residues of the fungicide pyraclostrobin (carbamic acid, [2-[[[1-(4-chlorophenyl)-1H- pyrazol-3-yl]oxy]methyl]phenyl]methoxy-, methyl ester) and its desmethoxy metabolite (methyl N-[[[1-(4-chlorophenyl)-1H-pyrazol-3-yl]oxy]methyl]phenyl carbamate), expressed as parent compound.

Pyraclostrobin tolerances for animal commodities are listed in 40 CFR §180.582 (a)(2) and are expressed in terms of the combined residues of the fungicide pyraclostrobin and its metabolites convertible to 1-(4-chlorophenyl)-1H-pyrazol-3-ol and 1-(4-chloro-2-hydroxyphenyl)-1H-pyrazol-3-ol, expressed as parent compound.

For petition (PP#8F7385), BASF has proposed a tolerance for the combined residues of pyraclostrobin and its desmethoxy metabolite in/on sorghum forage, grain, and stover at 5.0 ppm, 0.5 ppm, and 0.8 ppm, respectively. The submitted field trial data for sorghum forage, grain, and stover are adequate. The field trial data for these crops were entered into the Agency's tolerance spreadsheet as specified by the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP to determine appropriate tolerance levels. The tolerance spreadsheet recommends tolerances of 5.0 ppm for sorghum forage, 0.60 ppm for sorghum grain, and 0.80 ppm for sorghum stover.

For petition (PP#8F7390), BASF has proposed a tolerance for the combined residues of pyraclostrobin and its desmethoxy metabolite in/on stone fruit crop group at 2.5 ppm. The current EPA established tolerance for total residues of pyraclostrobin in the stone fruit crop group is 0.9 ppm in 40 CFR §180.582. The submitted field trial data for stone fruits are acceptable. The field trial data for stone fruits were entered into the Agency's tolerance spreadsheet as specified by the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP to determine appropriate tolerance levels. The tolerance spreadsheet recommends a tolerance of 2.5 ppm for stone fruits.

For petition (PP#8F7394), BASF has proposed a tolerance for the combined residues of pyraclostrobin and its desmethoxy metabolite in/on coffee green bean at 0.5 ppm. The submitted field trial data for coffee is adequate. The field trial data for coffee were entered into the Agency's tolerance spreadsheet as specified by the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP to determine appropriate tolerance levels. The tolerance spreadsheet recommends tolerances of 0.30 ppm for coffee. An acceptable coffee processing study has been submitted and the results suggest that no tolerances are required for the processed commodities of coffee.

Adequate cattle and poultry feeding studies are available. The existing pyraclostrobin tolerances for milk, meat, fat, meat byproducts except liver, and liver of cattle, goats, hogs, horses, and sheep were reassessed, and no adjustments are needed. Tolerances for eggs and poultry are not needed at this time based on data from the poultry feeding and metabolism studies [Category 180.6(a)(3)]. If, in the future, the petitioner proposes a use which increases the dietary burdens of poultry, then the Category 3 situation will be re-evaluated.

Refer to Section 11 for the detailed discussion of established Codex Alimentarius Commission (CAC) maximum residue limits (MRLs) for residues of pyraclostrobin, and for a comparison of Canadian and US tolerances.

A summary of the recommended tolerances for the crop commodities discussed in this document is presented in Table 12. The petitioner should submit a revised Section F reflecting the recommended tolerances and commodity definitions presented in Table 12.

TABLE 12. Tolerance Summary for Pyraclostrobin.

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Tolerances Proposed Under PP#8F7385			
Sorghum grain, forage	5.0	5.0	Sorghum, grain, forage.
Sorghum grain, grain	0.5	0.60	Sorghum, grain, grain.
Sorghum grain, stover	0.8	0.80	Sorghum, grain, stover. Adequate field trial data are available.
Tolerances Proposed Under PP#8F7390			
Fruit, stone, group 12	2.5	6.0	Fruit, stone group 12. Adequate field trial data are available.
Tolerances Proposed Under PP#8E7394			
Coffee	0.5	0.30	Coffee, green bean. Adequate field trial data are available.

5.2 Dietary Exposure and Risk

Reference: *Pyraclostrobin. Acute and Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments to Support New Use on Sorghum Grain (PP#8F7385); Increase of Tolerance for the Stone Fruit Crop Group 12 to satisfy European Union (EU) import requirement (PP#8F7390), and Establishment of a Permanent import Tolerance for Coffee (PP#8E7394); DP356194.drs; 04/01/09.*

Dietary risk assessment incorporates both exposure and toxicity of a given pesticide. The risk is expressed as a percentage of a maximum acceptable dose (i.e., the dose which HED has concluded will result in no unreasonable adverse health effects). This dose is referred to as the population adjusted dose (PAD). HED is concerned when estimated dietary risk exceeds 100% of the PAD.

DEEM-FCID™ Program and Consumption Information

Pyraclostrobin acute and chronic dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.03), which incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" (e.g., apple pie) are linked to EPA-defined food commodities (e.g. apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. For chronic exposure assessment, consumption data are averaged for the entire U.S. population and within population subgroups, but for acute exposure assessment are retained as individual consumption events. Based on analysis of the 1994-96, 98 CSFII consumption data, which took into account dietary patterns and survey respondents, HED concluded that it is most appropriate to report risk for the following population subgroups: the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, adults 20-49, females 13-49, and adults 50+ years old.

Acute Dietary (Food and Drinking Water) Exposure Results and Characterization

A slightly refined acute dietary exposure assessment was performed for pyraclostrobin. The analysis used tolerance level residues or highest field trial residues, 100% crop treated, and empirical processing factors. Experimentally derived processing factors were used for fruit juices, tomato and wheat commodities. For all other processed commodities, DEEM default processing factors were assumed. For acute exposures the peak concentration EDWC of 35.6 ppb was incorporated into the DEEM_FCID into the food categories "water, direct, all sources" and water, indirect, all sources"(based on a maximum application rate of 3.0 lb ai/A/season for the turf use rate).

The results of the acute dietary analysis for food and drinking water indicate that acute dietary risks do not exceed the Agency's level of concern (< 100% of the aPAD) for the U.S. population and all population subgroups; see Table 13. Combined dietary exposure from food and drinking water at the 95th percentile of exposure is estimated to be 0.044629 mg/kg/day for the U.S. population, which is equivalent to 1.5% of the acute Population Adjusted Dose (aPAD). The population subgroup with the highest estimated acute dietary exposure to pyraclostrobin is females 13-49 years, with an estimated exposure at the 95th percentile of 0.040558 mg/kg/day, equivalent to 81% of the aPAD.

Chronic Dietary (Food and Drinking Water) Exposure Results and Characterization

A moderately refined chronic dietary analysis was conducted for this assessment. The chronic dietary analysis included tolerance level or average field trial residues, average percent crop treated estimates when available, and empirical processing factors. Percent crop treated information from a screening level usage analysis (SLUA) of agricultural uses of pyraclostrobin, provided by the Biological & Economic Analysis Division (BEAD) (DP362519, 03/17/09, A. Grube) was incorporated into the exposure estimates. Experimentally derived processing factors were used for fruit juices, tomato and wheat commodities. For all other processed commodities, DEEM default processing factors were assumed. For chronic exposures the annual average concentration EDWC of 2.3 ppb was incorporated into the DEEM_FCID into the food categories "water, direct, all sources" and water, indirect, all sources"(based on a maximum application rate of 3.0 lb ai/A/season for the turf use rate).

The results of the refined chronic dietary analysis which represents for food and drinking water are below the Agency's level of concern for all population subgroups; see Table 13. The dietary exposure for food and drinking water is estimated at 0.002466 mg/kg/day for the general U.S. population and 7.3%, of the chronic Population Adjusted Dose (cPAD), and 0.008032 mg/kg/day (24%, of the cPAD) for children 1-2 yrs, the population subgroup with the highest estimated chronic dietary exposure to pyraclostrobin.

Table 13. Summary of Dietary Exposure and Risk for Pyraclostrobin – Food & Drinking Water.

	Acute Dietary (95th Percentile)		Chronic Dietary		Cancer	
Population Subgroup	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD	Dietary Exposure (mg/kg/day)	Risk
General U.S. Population	0.044629	1.5	0.002466	7.3	A separate quantitative cancer risk assessment was not conducted.	
All Infants (< 1 year old)	0.063464	2.1	0.003682	11		
Children 1-2 years old	0.076275	2.5	**0.008032**	**24**		
Children 3-5 years old	0.066159	2.2	0.005827	17		
Children 6-12 years old	0.047354	1.6	0.003323	9.8		
Youth 13-19 years old	0.035393	1.2	0.001908	5.6		
Adults 20-49 years old	0.039279	1.3	0.001875	5.5		
Adults 50+ years old	0.041963	1.4	0.002000	5.9		
Females 13-49 years old	**0.040558**	**81**	0.001717	5.1		

Conclusions

Acute and chronic exposures and risks do not exceed HED's level of concern for the U.S. population and for all relevant population subgroups. Of note is that contribution from drinking water is minimal. HED concludes that the acute and chronic exposure estimates are unlikely to underestimate actual acute or chronic exposure.

5.3 Anticipated Residue and Percent Crop Treated (%CT) Information

The acute analysis was conducted using tolerance level residues or the highest residues for all commodities. These tolerance level or highest residues were derived from field trial data conducted at the maximum application rate and minimum PHI permitted on the proposed or existing labels. For all commodities 100% crop treated was assumed. A limited number of experimentally derived processing factors (for fruit juices, tomato and wheat commodities) were used to refine the acute and chronic analyses.

The chronic dietary assessment was conducted using tolerance level residues for all crops except for coffee, sorghum grain, stone fruits crop group 12, apple, broccoli, celery, collard, grape, lettuce, citrus, pepper, mustard green and tomato where anticipated average residue values were derived from crop field trials. These field trials represent maximum application rates and minimum PHIs. Average percent crop treated estimates were used when available from a recent Screening Level Usage Analysis (SLUA). A limited number of experimentally derived processing factors (for fruit juices, tomato and wheat commodities) from pyraclostrobin processing studies were also used to refine the analysis.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

A product containing pyraclostrobin (i.e., Insignia®) is registered for application to residential turf grass and recreational sites. It may be applied to turf at rates ranging from 0.28 to 0.5 lb ai/A, at intervals of 14 to 28 days; and the maximum seasonal application rate is 3 lb ai/A. The residential exposure assessment was prepared in an HED memorandum dated 8/19/04 (D298017, K. O'Rourke). Residential and recreational turf applications are applied by professional pest control operators (PCOs) only, and therefore, residential handler exposures do not occur. There is, however, a potential for exposure to homeowners in residential settings from entering previously treated lawns where children might play and adults might work or play. As a result, risk assessments have been completed for postapplication scenarios. The short-term MOEs for each postapplication scenario resulted in MOEs above 100, and therefore are not of concern. For toddlers, the short-term dermal MOE is 180 (0.027 mg/kg/day) and the combined incidental oral MOE is 620 (0.009425 mg/kg/day; hand-to-mouth activities), and combined dermal and oral exposures result in and MOE of 140. Dermal and incidental oral exposures are combined because they share common toxic effects; i.e., decreased body weight gain and decreased food intake/efficiency. For adults, the short-term dermal MOE is 260 (0.019 mg/kg/day).

Recreational exposures to turf are expected to be similar to, or in many cases less than, those evaluated for residential postapplication exposure and risk; and therefore, a separate recreational exposure assessment was not conducted.

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for pyraclostrobin. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

7.0 Aggregate Risk Assessments and Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures from various sources, HED considers both the route and duration of exposure. Common effects (i.e., decreased body weight gain, food intake, and food efficiency) were seen in the studies selected to evaluate dietary, dermal and incidental oral ingestion exposures; and therefore, route-specific exposures can be aggregated.

Based on the proposed Section 3 food crop uses, aggregate assessments were conducted for acute and chronic dietary exposures (food + drinking water), and existing short-/intermediate-term residential exposures (i.e., chronic dietary, plus incidental oral and dermal exposures for kids, and chronic dietary, plus dermal exposures for adults). Both short- and intermediate-term exposures may occur during postapplication activities for adults and children. However, because the toxicity endpoints and points of departure are identical for short- and intermediate-term exposures, separate risk estimates for short- and intermediate-term exposures were not calculated.

To assess aggregate acute and chronic dietary risks, estimates of pesticide residues in drinking water (EDWCs) were incorporated directly into the dietary exposure analysis. **Refer to section 5.2 for these risk estimates.**

The short-/intermediate-term aggregate risk assessment takes into account average exposure estimates from dietary consumption of pyraclostrobin (food and drinking water) and non-occupational/residential uses (turf). Postapplication exposures from the use on turf are considered predominantly short-term (1-30 days). To calculate the short-/intermediate-term aggregate risk estimates, the chronic dietary exposure (food + drinking water) is added to the residential exposures using the inverse MOE methodology described below (see Table 14 below). The total combined MOE from dietary (food + water) and non-occupational/residential exposure is 120 for children 1-2 years old, which is not of concern to HED. For adults the total combined MOE is 230, which also is not of concern to HED. These aggregate exposure risk assessments are considered conservative estimates, that should not underestimate risks, because of the following inputs: 1) dietary inputs primarily used tolerance level residues; 2) crop specific (turf) screening level drinking water modeling data were used (i.e., Tier II surface water model); 3) maximum application rates and minimum application intervals were used; and 4) conservative SOPs and upper level estimates of exposure were employed.

Table 14. Short-/Intermediate Term Aggregate Risk Calculations

Population	Dermal Exposure			Oral Exposure				Total Combined MOE[2]
	NOAEL mg/kg/day	Exposure mg/kg/day	MOE[1]	NOAEL mg/kg/day	Incidental Oral Exposure mg/kg/day	Chronic Dietary (Food + Water) mg/kg/day	MOE[1]	
Children 1-2 yrs	5	0.027	180	5.8	0.009425	0.008032	330	120
Adults	5	0.019	260	5	NA	0.002466	2000	230

[1] The Level of Concern MOE is 100.
[2] Total Combined MOE = $1/ [(1/MOE_{Dermal}) + (1/MOE_{Oral})]$

8.0 Cumulative Risk Characterization/Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to pyraclostrobin and any other substances and pyraclostrobin does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that pyraclostrobin has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Pathway

Reference: *Pyraclostrobin: Occupational and Residential Exposure Assessment for Proposed New Use on Sorghum (Headline®) and Sorghum Seed Treatment* (Stamina™). *DP 359197; B. O'Keefe; 03/16/09.*

9.1 Short-/Intermediate-Term Handler Risk

Pyraclostrobin may be applied to sorghum foliage with aerial, chemigation, or groundboom equipment. Pyraclostrobin is applied to sorghum seeds using commercial seed treatment equipment. Handler exposure is expected to be short- or intermediate-term based on information provided on proposed labels.

Foliar Treatment

Occupational handlers may experience short- and intermediate-term exposure to pyraclostrobin while mixing/loading, applying, flagging, or performing other handler tasks to support application to sorghum. No chemical-specific handler exposure data were submitted in support of this use pattern. It is the policy of the HED to use data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented in PHED Surrogate Exposure Guide (8/98) to assess handler exposures when chemical-specific monitoring data are not available (HED Science Advisory Council for Exposure Draft Policy # 7, dated 1/28/99). The results are presented in Table 15.

Exposure Scenarios for Foliar Treatments
The quantitative exposure and risk assessment developed for occupational handlers involved in application to field-grown sorghum is based on the following exposure scenarios:

- Mixing/loading liquid concentrate to support aerial applications,
- Mixing/loading liquid concentrate to support chemigation applications,
- Mixing/loading liquid concentrate to support groundboom applications,
- Applying sprays with aircraft,
- Applying sprays with groundboom equipment, and
- Flagging to support aerial spray applications.

HED's level of concern for the MOE is defined by the uncertainty factors that are applied to the assessment. HED applies a 10X factor to account for inter-species extrapolation and a 10X factor to account for intra-species sensitivity. The total uncertainty factor that has been applied to the non-cancer risk assessment for pyraclostrobin is 100 for occupational exposure. Occupational exposure and risk resulting in MOEs greater than or equal to 100 will not be of concern to HED.

Agricultural Handlers

Summaries of the exposures and risks for handlers involved in application to field-grown sorghum are included in Table 12. The maximum application rate for each exposure scenario is presented as the worst case scenario. All handler scenarios resulted in MOEs greater than the level of concern (MOEs ≥ 100) at some level of mitigation.

The dermal risks to handlers are not a concern with baseline attire (i.e., long-sleeve shirt, long pants, shoes, and socks) for the following scenarios:

- applying sprays with groundboom equipment; and
- flagging to support aerial spray applications.

If chemical-resistant gloves are worn in addition to baseline attire, the dermal risks are not a concern for the following scenarios:

- mixing and loading liquid concentrates to support aerial applications;
- mixing and loading liquid concentrates to support chemigation; and
- mixing and loading liquid concentrates to support groundboom applications.

The inhalation risks to handlers are not a concern with baseline attire (no respirator) for the following scenarios:

- mixing and loading liquid concentrates to support chemigation;
- mixing and loading liquid concentrates to support groundboom applications;
- applying sprays with groundboom equipment; and
- flagging to support aerial spray applications.

If a respirator is worn, the inhalation risks are not a concern for the following scenario:

- mixing and loading liquid concentrates to support aerial applications.

Note: The respirator unit exposure value represents a NIOSH-approved respirator with a dust-mist filter with MSHA/NIOSH approval number prefix TC-21 or any N, R, P, or HE filter. Such a respirator is generally referred to as an 80% protection factor respirator, or a "quarter-face, cup-style dust/mist filtering respirator".

Only engineering control (enclosed cockpit) data are available to assess dermal and inhalation risks to handlers operating aircraft. The risks are not a concern for pilots using enclosed cockpits and wearing baseline attire and no respirator.

Table 15. Pyraclostrobin Agricultural Handler Exposures and Risks															
Exposure Scenario	Crop and Product	App. Rate[a] (lb ai/acre)	Area Treated Daily[b] (acres)	Unit Exposures[c]				Dermal Doses[d] and MOEs[e] (LOC MOE = 100)				Inhalation Doses[f] and MOEs[g] (LOC MOE = 100)			
				Baseline Dermal (mg/lb ai)	Baseline Inhalation (µg/lb ai)	Baseline Dermal Plus Gloves (mg/lb ai)	Inhalation 80% PF (µg/lb ai)	Baseline Dose[h] mg/kg/day	Baseline MOE	PPE-G Dose[i] mg/kg/day	PPE-G MOE	Baseline Dose mg/kg/day	Baseline MOE	D-M Respirator Dose[j] mg/kg/day	D-M Respirator MOE
Mixing/Loading Liquid Concentrates for Aerial Application	Sorghum	0.2	1,200	2.9	1.2	0.023	0.24	1.6	3.1	0.013	**390**	0.0041	56	0.00082	**280**
Mixing/Loading Liquid Concentrates for Chemigation Applications		0.2	350	2.9	1.2	0.023	0.24	0.47	11	0.0038	**1,300**	0.0012	**190**	0.00024	**960**
Mixing/Loading Liquid Concentrates for Groundboom Applications		0.2	200	2.9	1.2	0.023	0.24	0.27	18	0.0021	**2,300**	0.00069	**340**	0.00014	**1,700**
Applying Sprays via Aerial Equipment[k]		0.2	1,200	0.005 (Eng. Cont.)	0.068 (Eng. Cont.)	NA	NA	0.0028 (Eng. Cont.)	**1,800** (Eng. Cont.)	NA	NA	0.00023 (Eng. Cont.)	**990** (Eng. Cont.)	NA	NA
Applying Sprays via Groundboom		0.2	200	0.014	0.74	0.014	0.148	0.0013	**3,800**	0.0013	**3,800**	0.00042	**540**	0.000085	**2,700**
Flagging for Aerial Spray Applications		0.2	350	0.011	0.35	NA	0.07	0.0018	**2,800**	NA	NA	0.00035	**660**	0.00007	**3,300**

a. Application Rates based on proposed supplemental label for EPA Reg. No. 7969-186.
b. Science Advisory Council Policy # 9.1
c. Unit Exposures based on PHED Version 1.1
d. Dermal Dose (mg/kg/day) = daily unit exposure (mg/lb ai) x application rate (lb ai/acre) x acres treated * dermal absorption (14%) / body weight (60 kg adult female).
e. Dermal MOE = NOAEL (5.0 mg/kg/day) / dermal daily dose (mg/kg/day). Level of concern = 100.
f. Inhalation Dose (mg/kg/day) = daily unit exposure (µg/lb ai) x application rate (lb ai/acre) x acres treated * inhalation absorption (100%) x conversion factor (1 mg/1,000 µg) / body weight (70 kg).
g. Inhalation MOE = NOAEL (0.23 mg/kg/day) / inhalation daily dose (mg/kg/day). Level of concern = 100.
h. Baseline Dermal: Long-sleeve shirt, long pants, and no gloves; Baseline Inhalation: no respirator.
i. Baseline plus Gloves Dermal: Baseline plus chemical-resistant gloves.
j. D/M: The respirator unit exposure value represents a NIOSH-approved quarter-face, cup style dust/mist filtering respirator (e.g., dust mask), which is considered to provide an 80% reduction in inhalation exposure.
k. Only engineering control (enclosed cockpit) data are available to assess dermal and inhalation risks to handlers operating aircraft.

Seed Treatment
Occupational handlers may experience short- and intermediate-term exposure to pyraclostrobin while performing seed treatment activities in commercial settings. In addition, occupational secondary handlers may experience short- and intermediate-term exposure while planting pyraclostrobin-treated sorghum seeds. No chemical-specific handler exposure data were submitted in support of this use pattern. For assessing seed treatment and seed planting activities, unit exposure data were taken from HED Science Advisory Council for Exposure Policy 14: Standard Operating Procedures for Seed Treatment. The amount of active ingredient handled depends on the application rate (lb ai/100 lb seed) and the pounds of seed treated in a day (or the pounds of seed that can be planted in a day), all of which vary depending upon the seed type. Values for the amount of seed treated and planted per day were obtained from HED's Standard Operating Procedure (SOP) Policy 15. The results are presented in Table 16.

Exposure Scenarios for Seed Treatments
The quantitative exposure and risk assessment developed for occupational handlers involved in commercial application to sorghum seed is based on the following exposure scenarios:

- Loading the pesticide into seed treatment equipment and applying to sorghum seeds ("loader/applicator"),
- Loading seeds into bags ("bagger"),
- Sewing seed bags ("sewer"), and
- Handlers involved in multiple commercial seed treatment activities ("multiple activities")

In addition, a quantitative exposure/risk assessment was developed for occupational secondary handlers involved in planting treated sorghum seeds.

Commercial Seed Treatment Handlers
Summaries of the exposures and risks for handlers involved in commercial application to sorghum seed and planting treated sorghum seed are included in Table 13. The maximum application rate for each exposure scenario is presented as the worst case scenario. All seed treatment activities result in MOEs greater than the LOC of 100 and are not of concern at some level of risk mitigation.

The dermal risks to handlers are not a concern with baseline attire (i.e., long-sleeve shirt, long pants, shoes, and socks) for the following scenarios:

- loading treated seeds into bags ("bagger"), and
- sewing the bags of seed ("sewer")

There are no data to estimate dermal exposure and risk at baseline attire for the following scenarios:

- loading the pesticide into seed treatment equipment and applying to sorghum seeds ("loader/applicator");
- handlers involved in multiple commercial seed treatment activities ("multiple activities"); and
- planting treated seeds ("planter").

The dermal risks are not a concern at baseline attire plus chemical-resistant gloves for these scenarios.

The inhalation risks to handlers are not a concern at baseline attire (no respirator) for the following scenarios:

- loading the pesticide into seed treatment equipment and applying to sorghum seeds ("loader/applicator");
- loading treated seeds into bags ("bagger");
- sewing the bags of seed ("sewer"); and
- planting treated seeds ("planter").

If a respirator is worn in addition to baseline attire, inhalation risk is not a concern for the following scenario:

- handlers involved in multiple commercial seed treatment activities ("multiple activities").

Note: The respirator unit exposure value represents a NIOSH-approved respirator with a dust-mist filter with MSHA/NIOSH approval number prefix TC-21 or any N, R, P, or HE filter. Such a respirator is generally referred to as an 80% protection factor respirator, or a "quarter-face, cup-style dust/mist filtering respirator".

Table 16. Pyraclostrobin Seed Treatment Handler Exposures and Risks														
Exposure Scenario	lbs seed treated or planted per day[a]	Appl. Rate[b] (lb ai/100 lb	Unit Exposures[c]				Dermal Doses[g] and MOEs[h] (LOC MOE = 100)				Inhalation Doses[i] and MOEs[j] (LOC MOE = 100)			
			Dermal Baseline[d] (mg/lb ai)	Dermal PPE-G[e] (mg/lb ai)	Inhalation Baseline[f] (µg/lb ai)	D-M Respirator (µg/lb ai)	Baseline Dose	Baseline MOE	PPE-G Dose	PPE-G MOE	Baseline Dose	Baseline MOE	D-M Respirator Dose	D-M Respirator MOE
Sorghum														
Loader/ Applicator	718,000	0.02	No Data	0.023	0.34	0.068	No Data	No Data	7.70E-3	**650**	6.97E-4	**330**	1.39E-4	**1,600**
Sewer			0.0062	No Data	0.23	0.046	2.10E-3	**2,400**	No Data	No Data	4.72E-4	**490**	9.44E-5	**2,400**
Bagger			0.0091	No Data	0.16	0.032	3.00E-3	**3,600**	No Data	No Data	3.28E-4	**700**	6.56E-5	**3,500**
Multiple Activities			No Data	0.042	1.6	0.32	No Data	No Data	1.40E-2	**360**	3.28E-3	70	6.56E-4	**350**
Planter (Secondary Handler)	12,000	0.02	No Data	0.25	3.4	0.68	No Data	No Data	1.40E-3	**3,600**	1.20E-4	**2,000**	2.72E-5	**8,500**

a. The amount of seed treated or planted per day are HED estimates based on HED Science Advisory Council for Exposure Policy 15: Amount of Seed Treated or Planted per Day, March 2, 2004, and values submitted by industry.
b. Application rates are the maximum application rates determined from proposed labels for pyraclostrobin.
c. The unit exposures are from HED Science Advisory Council for Exposure Policy 14: Standard Operating Procedures for Seed Treatment. For the tuberous and corm vegetable commercial seed treatment scenario, however, the unit exposures are from the Pesticide Handlers Exposure Database (PHED) Version 1.
d. Dermal Baseline: Long-sleeve shirt, long pants, and no gloves.
e. Dermal PPE-G: Baseline plus chemical-resistant gloves.
f. Inhalation Baseline: no respirator.
g. D/M: The respirator unit exposure value represents a NIOSH-approved quarter-face, cup style dust/mist filtering respirator (e.g., dust mask), which is considered to provide an 80% reduction in inhalation exposure.
h. Dermal Dose (mg/kg/day) = daily unit exposure (mg/lb ai) x application rate (lb ai/lb seed) x lbs seed treated or planted per day x dermal absorption (14%) / body weight (60 kg, adult female).
i. Dermal MOE = NOAEL (5 mg/kg/day) / dermal daily dose (mg/kg/day). Level of concern = 100.
j. Inhalation daily dose (mg/kg/day) = daily unit exposure (µg/lb ai) x (lb ai/lb seed) x lbs seed treated or planted per day x conversion factor (1 mg/1,000 µg) / body weight (70 kg).
k. Inhalation MOE = NOAEL (0.23 mg/kg/day) / inhalation daily dose (mg/kg/day). Level of concern = 100.

9.2 Short-/Intermediate-Term Postapplication Risk

One of the proposed uses for pyraclostrobin involves foliar applications to field-grown sorghum. Therefore, postapplication exposure is possible for workers entering treated fields for activities such as scouting, irrigating, and hand weeding. There are also potential postapplication exposures to workers entering fields after pyraclostrobin-treated sorghum seeds are planted.

HED assumes that inhalation exposures are minimal compared to dermal exposures following outdoor applications of an active ingredient with low vapor pressure. Since pyraclostrobin is applied only in outdoor settings and has a very low vapor pressure, postapplication inhalation exposures and risks were not assessed.

Postapplication dermal exposure and risk was estimated. Chemical-specific dislodgeable foliar residue (DFR) data had previously been submitted by the registrant to support earlier registration requests for food crops (MRID#s: 45118727, 45118724, 45118726, and 45118728 and 45118729). A summary of the results and an overview of each study was provided in a previous assessment (D269670, K. O'Rourke, 9/30/2002).

The DFR data were used to estimate restricted entry intervals (REIs) by extrapolating to the proposed use on sorghum. It was found that the type of formulation used influences the DFR profile. Since the proposed product is an EC formulation, the DFR data for the liquid concentrate formulations were considered. Average percent initial DFR values were calculated (i.e., 18% for liquid concentrates) and used to estimate surrogate residue values for field-grown sorghum. Although uncertainties are introduced into the assessment when crop-specific residues are used to estimate residues for other types of crops, it is believed to be more realistic than using default assumptions.

In addition to these residue data, transfer coefficients (Tc) are used to relate the foliage residue values to activity patterns (e.g., scouting) to estimate potential human exposure. The transfer coefficients used in this assessment are from an interim transfer coefficient policy developed by HED's Science Advisory Council for Exposure using proprietary data from the Agricultural Re-entry Task Force (ARTF) database (policy # 3.1).

The postapplication exposure and risk associated with sorghum crops is summarized in Table 17. All scenarios resulted in MOEs greater than 100 on day 0 (12 hours after application), and therefore are not of concern to HED. Since the postapplication risks are not a concern on Day 0 (12 hours following application), the restricted entry interval (REI) is based on the acute toxicity of pyraclostrobin technical material which is classified as Category III for acute dermal toxicity and for skin and eye irritation potential. Pyraclostrobin is not a dermal sensitizer. Under the Worker Protection Standard for Agricultural Pesticides, the default restricted-entry interval is 12 hours for active ingredients classified as acute toxicity categories III or IV for these routes of entry.

Potential postapplication exposures and risks to workers entering fields after pyraclostrobin-treated sorghum seeds are planted were not quantitatively assessed. HED believes that the 12-hour restricted-entry interval established for foliar uses on sorghum is sufficiently protective for workers entering fields following planting of treated seeds. Note: A standard WPS exception to this REI states that once seeds are planted in soil or other planting media, the Worker Protection Standard allows workers to enter the treated area without restriction if there will be no worker contact with the seeds or the soil/media subsurface.

For the seed treatment uses, the pyraclostrobin labeling should state:

"Seed that has been treated with this product that is then packaged or bagged for future use must contain the following labeling on the outside of the seed package or bag."

"Treated Seed - Do Not Use for Food, Feed, or Oil Purposes."

"When opening this bag or loading/pouring the treated seed, wear long-sleeved shirt, long pants, shoes, socks, and chemical resistant gloves."

"After the seeds have been planted, do not enter or allow worker entry into treated areas during the restricted-entry interval (REI) of 12 hours. Exception: Once the seeds are planted in soil or other planting media, the Worker Protection Standard allows workers to enter the treated area without restriction if there will be no worker contact with the soil/media subsurface."

Table 17. Summary of Postapplication Risks for Proposed Use on Field-Grown Sorghum

Crop	Application Rate (lb ai/A) [1]	DAT [2]	DFR [3] (µg/cm²)	TC [4] (cm²/hr)	Activity [4]	Short- & Intermediate-Term Dose [5]	Short- & Intermediate-Term MOE [6]
Sorghum	0.20	0	0.404	100	Scouting and hand weeding of low growth foliage plants	0.00075	6,600
				1,000	Irrigating and scouting of high growth foliage plants	0.0075	660

1 Maximum application rate indicated on proposed label (see Table 2).
2 DAT = Days after treatment needed to reach the LOC of 100; DAT 0 = the day of treatment, after sprays have dried; assumed to be approximately 12 hours.
3 DFR (µg/cm²) = Application rate (lb ai/A) x CF (4.54E+8 ug/lb) x CF (2.47E-8 A/cm²) x Initial Fraction of ai Retained on the Foliage (from Table 6, used LC average [18%]). This data was

derived from summaries of results presented in MRIDs 45118727, 45118724, 45118726, and 45118728 and 45118729.

4 TC (cm^2/hr) = transfer coefficients and associated activities from ExpoSAC Policy Memo #003.1 "Agricultural Transfer Coefficients", 8/17/2000.

5 Daily Dose = [(DFR x TC x 14% Dermal absorption x 8-hr Exposure Time)] / [(CF: 1000 µg/mg) x (60-kg Body Weight)] Short-/intermediate-term Dermal NOAEL = 5 mg/kg/day. The LOC is 100.

6 MOE = NOAEL/Daily Dose

10.0 Data Needs and Label Recommendations

10.1 Toxicology Data Needs

870.7800 Immunotoxicity study

As part of the new 40CFR §158 Guidelines, an immunotoxicity study in rats and/or mice is required (see Appendix B).

10.2 Residue Chemistry Data Needs and Label Recommendations

For Petitions #8F7385, #8F7390, and #8F7394

860.1550 Proposed Tolerances

The petitioner should submit revised Section Fs reflecting the recommended tolerances and commodity definitions presented in Table 9.

10.3 Occupational Label Recommendations

Stamina™ BAS 500 12 F Label

For the scenario of handlers involved in multiple commercial seed treatment activities ("multiple activities"), a dust mist respirator is needed to achieve an MOE ≥ 100, which is not already included on the proposed Stamina™ label.

For the seed treatment uses, the pyraclostrobin seed treatment labeling should be required to add specific statements regarding the personal protective equipment required for persons planting treated seed as well as other label restrictions, as follows:.

- "Seed that has been treated with this product that is then packaged or bagged for future use must contain the following labeling on the outside of the seed package or bag."
- "Treated Seed - Do Not Use for Food, Feed, or Oil Purposes."
- "When opening this bag or loading/pouring the treated seed, wear long-sleeved shirt, long pants, shoes, socks, and chemical resistant gloves."

- "After the seeds have been planted, do not enter or allow worker entry into treated areas during the restricted-entry interval (REI) of 12 hours. Exception: Once the seeds are planted in soil or other planting media, the Worker Protection Standard allows workers to enter the treated area without restriction if there will be no worker contact with the soil/media subsurface."

Headline® Fungicide Label

For the use on sorghum, the scenario of mixing and loading liquid concentrates to support aerial applications, a dust mist respirator is needed to achieve an MOE ≥ 100, which is not already included on the proposed Headline® label.

11.0 International Residue Limit Status

The Codex Alimentarius Commission (CAC) has established maximum residue limits (MRLs) for residues of pyraclostrobin on stone fruit and coffee beans. The residue definitions are not harmonized. The CAC definition contains parent only, whereas the US residue definition includes a metabolite. The MRL values are harmonized for coffee beans, but the MRL values for stone fruits are not. The CAC value for stone fruits of 1 mg/kg is based on evaluation of US residue data for cherries, where the highest residue was 0.63 mg/kg. The recommended US tolerance of 2.5 ppm results from new trials conducted in 2007 on cherries, peaches, and plums using a WDG formulation of pyraclostrobin and boscalid (M. Negussie, D359194). Use of this particular formulation requires an increase in the US tolerance from its present value of 0.9 ppm (40 CFR 180.582) because measured residues were as high as 1.9 ppm.

Canada has established tolerances for various stone fruits at 0.7 ppm. The US and Canadian residue definitions are harmonized. The US tolerance for stone fruits is higher than the Canadian tolerances for individual stone fruit commodities because of the new formulation uses.

<table>
<tr><td colspan="4">INTERNATIONAL RESIDUE LIMIT STATUS</td></tr>
<tr><td>Chemical Name: methyl [2-[[[1-(4-chlorophenyl)-1H-pyrazol-3-yl]oxy]methyl]phenyl]methoxy carbamate</td><td>Common Name: Pyraclostrobin</td><td>☒ Proposed tolerances
☒ Reevaluated tolerance
☐ Other</td><td>Date: 03/19/2009</td></tr>
<tr><td colspan="2">Codex Status (Maximum Residue Limits)</td><td colspan="2">U. S. Tolerances</td></tr>
<tr><td colspan="2">☐No Codex proposal step 6 or above
☐No Codex proposal step 6 or above for the crops requested</td><td colspan="2">Petition Numbers: PP#8F7385, PP#8F7390, PP#8E7394
DP#359194
Other Identifier:</td></tr>
<tr><td colspan="2" rowspan="2">Residue definition (step 8/CXL): pyraclostrobin</td><td colspan="2">Reviewers/Branch: M. Negussie, T. Morton, L. Cheng</td></tr>
<tr><td colspan="2">Residue definition in PP#8F7385, PP#8F7390, and PP#8E7394: Combined residues of pyraclostrobin and BF 500-3, expressed as pyraclostrobin.</td></tr>
<tr><td>Crop (s)</td><td>MRL (mg/kg)</td><td>Crop (s)</td><td>Recommended Tolerance (ppm)</td></tr>
<tr><td></td><td></td><td colspan="2">PP#8F7385</td></tr>
<tr><td></td><td></td><td>Sorghum, grain, forage</td><td>5.0</td></tr>
<tr><td></td><td></td><td>Sorghum, grain, grain</td><td>0.6</td></tr>
<tr><td></td><td></td><td>Sorghum, grain, stover</td><td>0.8</td></tr>
<tr><td></td><td></td><td>PP#8F7390</td><td></td></tr>
<tr><td>Stone Fruits</td><td>1.</td><td>Fruits, Stone, group 12</td><td>2.5</td></tr>
<tr><td></td><td></td><td colspan="2"></td></tr>
<tr><td></td><td></td><td>PP#8F7394</td><td></td></tr>
<tr><td>Coffee beans</td><td>0.3</td><td>Coffee, bean, green</td><td>0.3</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="2">Limits for Canada</td><td colspan="2">Limits for Mexico</td></tr>
<tr><td colspan="2">☐No Limits
☐No Limits for the crops requested</td><td colspan="2">xNo Limits
☐No Limits for the crops requested</td></tr>
<tr><td colspan="2">Residue definition:
plant: methyl [2-[[[1-(4-chlorophenyl)-1H-pyrazol-3-yl]oxy]methyl]phenyl]methoxycarbamate, including the metabolite [2-[[[1(4-chlorophenyl)-1H-pyrazol -3-yl]oxy]methyl]phenyl]carbamate

livestock: methyl [2-[[[1-(4-chlorophenyl)-1H-pyrazol-3-yl]oxy]methyl]phenyl]methoxycarbamate, including the metabolites convertible to 1-(4-chlorophenyl)-1H-pyrazol-3-ol and 1-(4-chloro-2-hydroxyphenyl)-1H-pyrazol-3-ol</td><td colspan="2">Residue definition: N/A</td></tr>
<tr><td>Crop (s)</td><td>MRL (mg/kg)</td><td>Crop (s)</td><td>MRL (mg/kg)</td></tr>
<tr><td>Apricot</td><td>0.7</td><td></td><td></td></tr>
<tr><td>Nectarines</td><td>0.7</td><td></td><td></td></tr>
<tr><td>Peaches</td><td>0.7</td><td></td><td></td></tr>
<tr><td>Plumcots</td><td>0.7</td><td></td><td></td></tr>
<tr><td>Plums</td><td>0.7</td><td></td><td></td></tr>
<tr><td>Prune plums</td><td>0.7</td><td></td><td></td></tr>
<tr><td>Sweet cherries</td><td>0.7</td><td></td><td></td></tr>
<tr><td>Tart cherries</td><td>0.7</td><td></td><td></td></tr>
<tr><td colspan="4">S.Funk, 03/31/2009.</td></tr>
</table>

12.0 Appendix A: Toxicity Profile

12.1 Appendix A1. Pyraclostrobin Toxicology Requirements and Available Studies for Food Uses

Appendix A1: Pyraclostrobin Toxicology Requirements and Available Studies for Food Uses.

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (dog)	yes	yes
870.3200	28-Day Dermal	yes	yes
870.3465	28-Day Inhalation	yes	yes
870.3700a	Developmental Toxicity (rat)	yes	yes
870.3700b	Developmental Toxicity (rabbit)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rat)	yes	yes
870.4100b	Chronic Toxicity (dog)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5395	Mutagenicity—Microneucleus - mammalian	yes	yes
870.5550	Mutagenicity—Unscheduled DNA - mammalian	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	-
870.6100b	90-Day Neurotoxicity (hen)	no	-
870.6200a	Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b	90 Day Neuro. Screening Battery (rat)	yes	yes
870.6300	Develop. Neuro	no	-
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	yes	yes
870.7800	Immunotoxicity	yes	no

12.2 Appendix A2.: Acute Toxicity Data on Pyraclostrobin Technical

Appendix A2. Acute Toxicity Profile:

Acute Toxicity Data on Pyraclostrobin Technical

Study/ Species	MRID	Results	Toxicity Category
870.1100 Acute Oral, Rats	45118302	LD_{50} = > 5000 mg/kg	IV
870.1200 Acute Dermal, Rabbits	45118305	LD_{50} = >2000mg/kg	III
870.1300 Acute Inhalation, Rats	45118308	0.31 mg/L < LC_{50} < 1.07 mg/L	II
870.2400 Primary Eye Irritation, Rabbits	45118311	Moderate eye irritation; MAS 4.6/110	III
870.2500 Primary Skin Irritation, Rabbits	45118314	Moderate skin irritation; MAS 2.2/8.0	III
870.2600 Dermal Sensitization, Guinea pig	45118317	Not a skin sensitizer	N/A

12.3 Appendix A3.: Subchronic, Chronic and Other Toxicity Profile

Appendix A3. Subchronic, Chronic and Other Toxicity Profile		
Guideline No./Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
870.3100 90-Day oral toxicity (rat)	45118321 (1999) Acceptable/guideline 0, 50, 150, 500, 1000, 1500 ppm M: 0, 3.5, 10.7, 34.7, 68.8, 105.8 mg/kg/day; F: 0, 4.2 12.6, 40.8, 79.7,118.9 mg/kg/day	NOAEL = 10.7 mg/kg/day LOAEL = 34.7 mg/kg/day based on ↓body weight/ weight gain in males, ↓food intake (both sexes), ↑ relative liver wt and spleen wt in females and histopathology of duodenum and liver in males, and spleen in both sexes.
870.3100 90-Day oral toxicity (mouse)	45118320 (1999) Acceptable/guideline 0, 50, 150, 500, 1000, 1500 ppm M: 0, 9.2, 30.4, 119.4, 274.4, 475.5 mg/kg/day F:0, 12.9, 40.4, 162.0, 374.1, 634.8 mg/kg/day	NOAEL = 9.2 mg/kg/day LOAEL = 30.4 mg/kg/day based on ↓body weight/ weight gain in males, changes in clinical chemistry in both sexes (increased urea and decreased triglycerides), and increased incidences in females of lymph node apoptosis, thymus atrophy, and ulcer/erosion in the glandular stomach.
870.3150 90-Day oral toxicity (dog)	45118323 (1999) Acceptable/guideline 0, 100, 200, 450 ppm M: 0, 2.8, 5.8, 12.9 mg/kg/day F: 0, 3.0, 6.2, 13.6 mg/kg/day	NOAEL = 5.8 mg/kg/day LOAEL = 12.9 mg/kg/day based on ↑diarrhea, clinical chem. changes, and increased incidence of thickening/ mucosal hypertrophy of the duodenum in both sexes; body weight loss, and ↓food intake/efficiency in females.
870.3050 28-Day oral toxicity (rat)	MRID 45118322 (1999) Acceptable/guideline 0, 20, 100, 500, 1500 ppm M: 0, 1.8, 9.0, 42.3, 120.2 mg/kg/day F: 0, 2.0 9.6, 46.6, 126.3 mg/kg/day	NOAEL = 9.0 mg/kg/day LOAEL = 42.3 mg/kg/day based on changes in hematology parameters, increased absolute and relative spleen weight, histopathology in spleen and liver, in addition to increased duodenal mucosal hyperplasia in both sexes.
870.3200 28-Day dermal toxicity (rat)	45118324 (1999) Unacceptable/guideline (a higher dose could be tolerated and the limit dose is 1000 mg/kg/day) 0, 40, 100, 250 mg/kg for 5 days/wk	Dermal NOAEL = 40 mg/kg/day Dermal LOAEL = 100 mg/kg/day based on scale formation, hyperkeratosis, and epidermal thickening. Systemic NOAEL = 250 mg/kg/day Systemic LOAEL > 250 mg/kg/day The HIARC (TXR 0051553) determined that a repeat study at a higher dose is not needed since an oral end-point (developmental toxicity NOAEL of 5.0 mg/kg/day) with a 14% dermal absorption rate yields a dermal equivalent dose of 36 mg/kg/day (5 ÷ 0.14) which is well below the apparent systemic toxicity NOAEL of 250 mg/kg/day in the dermal study.

Appendix A3. Subchronic, Chronic and Other Toxicity Profile		
Guideline No./Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
870.3465 28-Day inhalation toxicity (rat)	46638801 (2005) Acceptable/guideline 0.001, 0.030, or 0.300 mg/L for 6 hours per day, 5 days/week (20 exposure days) – Test substance was dissolved in acetone and administered as an aerosol	Inhalation NOAEL = 0.001 mg/L (oral equivalent dose = 0.23 mg/kg/day) Inhalation LOAEL = 0.030 mg/L (oral equivalent dose = 6.9 mg/kg/day) based on findings of hyperplasia in the duodenum, alveolar histiocytosis in the lungs, and olfactory atrophy/necrosis in the nasal tissues.
870.3700a Prenatal developmental (rat)	45118325 (1999) Acceptable/guideline 0, 10, 25, 50 mg/kg/day	**Maternal** NOAEL = 10 mg/kg/day LOAEL = 25 mg/kg/day based on ↓body wt/ wt gain and ↓food intake/efficiency. **Developmental** NOAEL = 25 mg/kg/day LOAEL = 50 mg/kg/day based on ↑ incidences of dilated renal pelvis and cervical ribs with no cartilage.
870.3700b Prenatal developmental (rabbit)	45118326 and 45437001 (1999) Acceptable/guideline 0, 1, 3, 5, 10, 20 mg/kg/day	**Maternal** NOAEL = 5 mg/kg/day LOAEL = 10 mg/kg/day based on ↓ body wt gain and ↓food intake/efficiency. **Developmental** NOAEL = 5 mg/kg/day LOAEL =10 mg/kg/day based on ↑ resorption/post-implantation loss.
870.3800 Reproduction and fertility effects (rat)	**Two Generation**: MRID 45118327 (1999) Acceptable/guideline when combined with the one generation preliminary study (below) 0, 25, 75, 300 ppm F_0 M/F: 0, 2.5/2.6, 7.4/7.8, 29.0/30.4 mg/kg/day F_1 M/F: 0, 2.8/3.0, 8.6/9.0, 35.0/36.0 mg/kg/day **One Generation**: MRID 45596210 (2002) 0, 200, 400, 600 ppm F_0 M/F: 0, 20.5/21.3, 39.9/42.5, 59.1/60.4 mg/kg/day	**Parental/Systemic** NOAEL = 29 mg/kg/day LOAEL > 29 mg/kg/day based on no effects. **Reproductive** NOAEL = 29 mg/kg/day LOAEL > 29 mg/kg/day based on no effects. **Offspring** NOAEL = 29 mg/kg/day LOAEL > 29 mg/kg/day based on no effects. **Offspring** NOAEL < 20.5 mg/kg/day **Offspring** LOAEL = 20.5 mg/kg/day based on decreased pup body weight and body weight gain on and after post-natal day 7.
870.4100a Chronic toxicity (rat)	45118329 (1999) Unacceptable/guideline 0, 25, 75, 200 ppm M: 0, 1.1, 3.4, 9.0 mg/kg/day F: 0, 1.5, 4.6, 12.3 mg/kg/day	NOAEL = 9.0 mg/kg/day LOAEL > 9.0 mg/kg/day.
870.4100b Chronic toxicity (dog)	45118328 (1999) Acceptable/guideline 0, 100, 200, 400 ppm M: 0, 2.7, 5.4, 10.8 mg/kg/day F: 0, 2.7, 5.4, 11.2 mg/kg/day	NOAEL = 5.4 mg/kg/day LOAEL = 10.8 mg/kg/day based on ↑ diarrhea and clinical chemistry changes in both sexes (decreased cholesterol, protein, albumin, and globulin), and ↓ body weight gain and ↓food intake/efficiency in females.

Appendix A3. Subchronic, Chronic and Other Toxicity Profile		
Guideline No./Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
870.4200 Carcinogenicity (rat)	45118331 (1999) Acceptable/guideline 0, 25, 75, 200 ppm M: 0, 1.2, 3.4, 9.2 mg/kg/day F: 0, 1.5, 4.7, 12.6 mg/kg/day	NOAEL = 3.4 mg/kg/day LOAEL = 9.2 mg/kg/day based on ↓ body weight and body weight gain, and kidney atrophy/tubular casts in both sexes; hepatic necrosis and gross/ microscopic ulcerations/lesions in the glandular and fore-stomachs in males. **No evidence of carcinogenicity**
870.4300 Carcinogenicity (mouse)	45118330 (1999) Unacceptable/guideline M: 0, 10, 30, 120 ppm 0, 1.4, 4.1, 17.2 mg/kg/day F: 0, 10, 30, 120, 180 ppm 0, 1.6, 4.8, 20.5, 32.8 mg/kg/day	NOAEL = M: 4.1 mg/kg/day F: 32.8 mg/kg/day LOAEL = M: 17.1 mg/kg/day based on decrease in body weight gain (20%) at 13 weeks which was supported by the results of a 90-day study. F >32.8 mg/kg/day Inadequate dosing in females based on CARC Report dated 10/22/03 (TXR # 0051445) **No evidence of carcinogenicity**
Gene Mutation 870.870.5100 Bacterial reverse mutation assay	45118332 (1997) Acceptable/guideline	**Negative** ± S9 up to 5,000 µg/plate by standard plate and tube preincubation. No cytotoxicity at any dose but there was precipitation at ≥2,500 µg/plate.
Gene Mutation 870.5300 Mammalian cell culture	45118335 (1998) Acceptable/guideline	**Negative** ± S9 up to cytotoxic and precipitating concentration of 20 µg/mL
Cytogenetics (*in vitro*) 870.5375 Chromosomal aberrations	45118333 (1999) Acceptable/guideline	**Negative** ± S9 for clastogenic/aneugenic activity up to 25 µg/mL. Precipitation and cytotoxicity (reduced cell attachment and poor quality of metaphases) were seen at concentrations ≥50 µg/mL.
Cytogenetics 870.5395 Micronucleus test in mouse	45118334 (1998) Acceptable/guideline	**Negative** for clastogenic/aneugenic activity up to the highest dose tested (300 mg/kg). In a preliminary study, doses ≥400 mg/kg caused death.
Unscheduled DNA synthesis 870.5550 Rat hepatocyte culture	45118336 (1998) Acceptable/guideline	**Negative** up to a cytotoxic concentration of 1.0 µg/mL.
870.6200a Acute neurotoxicity screening (rat)	45118337(1999) Acceptable/guideline 0, 100, 300, 1000 mg/kg	**Neurotoxicity** NOAEL = 1000 mg/kg M/F LOAEL >1000 mg/kg **Systemic** M/F NOAEL = 300/1000 mg/kg M/F LOAEL 1000/ >1000 mg/kg based on ↓body weight gain in males.

Appendix A3. Subchronic, Chronic and Other Toxicity Profile		
Guideline No./Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
870.6200b Subchronic neurotoxicity screening (rat)	45118401 (1999) Acceptable/guideline 0, 50, 250, 750 (M)/1500 (F) ppm M: 0, 3.5, 16.9, 49.9 mg/kg/day F: 0, 4.0, 20.4, 111.9 mg/kg/day	**Neurotoxicity** M/F NOAEL = 49.9/111.9 mg/kg/day M/F LOAEL >49.9/111.9 mg/kg/day. **Systemic** M/F NOAEL = 16.9/20.4 mg/kg/day M/F LOAEL = 49.9/111.9 mg/kg/day based on ↓ body weight gain, and ↓ food intake/efficiency.
870.7485 Metabolism and pharmacokinetics (rat)	45118403 (1998) 45118404 (1999) Acceptable/guideline	Nearly 35% of an oral dose of pyraclostrobin is absorbed with urinary and fecal excretions accounting for about 15% and 85%, respectively, and bile elimination accounted for about 30%. Two peak plasma concentrations were reached at 0.5-1 and 8 hours with lower plasma concentrations in males than females (by 16-38%) during the early peak phase. Elimination was biphasic at a low dose with plasma half lives of nearly 10/35 hours and monophasic at a high dose with a half-life of nearly 20 hours. Tissue distribution was fast, peaking at 0.5 hours, and was slightly higher among females. Some of the highest concentrations were found in the liver, thyroid, kidney, lung, adrenal glands, and pancreas but all levels dropped by more than 20-fold within 72 hours. About 33 metabolites were identified in urine, feces, and bile with no sex- or dose-related differences but the position of the label seemed to alter the profile, particularly in the urine. Desmethoxy pyraclostrobin (500M07) is one of the major metabolites in rat and is also found in large amounts in plants (BF 500-3) and livestock (500M07). The rat metabolic pathway included phase-I reactions such as N-demethoxylation, various hydroxylations, and cleavage of the ether bond with subsequent oxidation; these reactions were followed by phase II glucuronidation and sulfation.
870.7600 Dermal penetration (rat)	45118402 (1999) Unacceptable/guideline (most of the test material was retained on the dressing and was unavailable for absorption; therefore, actual dose cannot be determined.	The HIARC calculated and recommended a dermal penetration rate of 14% (report dated 2/10/03; TXR # 0051553)

13.0 Appendix B: Rationale for Toxicity Data Requirement

APPENDIX B: RATIONALE FOR TOXICITY DATA REQUIREMENTS

OPPTS Guideline Number: 870.7800 **Study Title: Immunotoxicity**
Rationale for Requiring the Data
The immunotoxicity study is a new data requirement under 40CFR §158 as a part of the data requirements for registration of a pesticide (food and non-food uses). The Immunotoxicity Test Guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing, and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (such as suppression) on the immune system. Immunosuppression is a deficit in the ability of the immune system to respond to a challenge of bacterial or viral infections, such as tuberculosis (TB), Severe Acquired Respiratory Syndrome (SARS), or neoplasia. Because the immune system is highly complex, studies not specifically conducted to assess immunotoxic endpoints are inadequate to characterize a pesticide's potential immunotoxicity. While data from hematology, lymphoid organ weights, and histopathology in routine chronic or subchronic toxicity studies may offer useful information on potential immunotoxic effects, these endpoints alone are insufficient to predict immunotoxicity.
Practical Utility of the Data
How will the data be used? Immunotoxicity studies provide critical scientific information needed to characterize potential hazard to the human population on the immune system from pesticide exposure. Since epidemiologic data on the effects of chemical exposures on immune parameters are limited, and are inadequate to characterize a pesticide's potential immunotoxicity in humans, animal studies are used as the most sensitive endpoint for risk assessment. These animal studies can be used to select endpoints and doses for use in risk assessment of all exposure scenarios, and are considered a primary data source for reliable reference dose calculation. For example, animal studies have demonstrated that immunotoxicity in rodents is one of the more sensitive manifestations of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) among developmental, reproductive and endocrinologic toxicities. Additionally, the EPA has established an oral reference dose (RfD) for tributyltin oxide (TBTO), based on observed immunotoxicity in animal studies (IRIS, 1997). **How could the data impact the Agency's future decision-making?** If the immunotoxicity study shows that the test material poses either a greater or a diminished risk than that given in the interim decision's conclusion, the risk assessments for the test material may need to be revised to reflect the magnitude of potential risk derived from the new data. If the Agency does not have these data, a 10X database UF may be applied for conducting a risk assessment from the available studies.